PATENT SPECIFICATION (11) 1253741

1253741

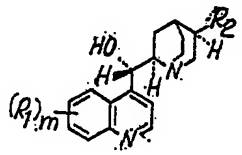
NO DRAWINGS

(21) Application No. 33311/69 (22) Filed 2 July 1969
(31) Convention Application No. 741913 (32) Filed 2 July 1968 in
(33) United States of America (US)
(45) Complete Specification published 17 Nov. 1971
(51) International Classification C 07 d 43/24 A 61 k 27/00//C 07 d 57/00 29/12
(52) Index at acceptance
C2C 172—194—284 1E3K4 1E5K4 1E6K4 1E7C2 1E7E1 1E7F2 1E7J 1E7N5 215 220 22Y 250 251 25Y 315 31Y 351 355 366 368 3A10E3D1 3A10E5E 3A12A4A 3A12B3 3A12B4 3A12C1 3A12C2 3A12C5 3A12C6 3A13A3A4 3A13A3B2 3A13A3C 3A13A3D 3A13AH1 3A13C10F 3A13C10G 3A13C10H 3A13C1C 3A13C6C 3A13C9 3A14A3D 3A14A5 3A14A6 3A14A8B 3A14A8C 3A19A4 3A19B2 3A19C2 3A19C3 3A19D3 3A8A4 3A8B2 3A8C3 3A8C6 3A8K 449 659 JA

(54) A PROCESS FOR THE MANUFACTURE OF QUINOLINE DERIVATIVES

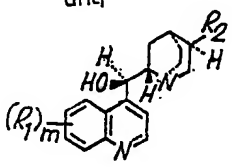
(71) We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with a process for the manufacture of quinoline derivatives of the general formulae



I

and



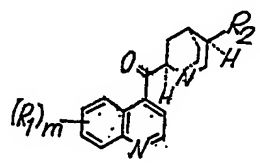
II

wherein R_1 is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or methylenedioxy, R_2 is lower alkyl or lower alkenyl and m is the integer 1 or 2, with the proviso that when R_1 is methylenedioxy m is the integer 1,
of their antipodes or racemates and acid addition salts thereof.

The term "lower alkyl" as used herein denotes a hydrocarbon group containing 1—7 carbon atoms, such as methyl, ethyl, propyl and butyl; ethyl is preferred. The term "lower alkoxy" denotes a lower alkyl ether group in which the lower alkyl moiety is described as above. The term "lower alkenyl" as used herein denotes a hydrocarbon group containing 2—7 carbon atoms, such as vinyl, propenyl and butenyl. Preferred is vinyl. The term "halogen" as will be used hereinafter denotes all of the halogens, i.e., bromine, chlorine, fluorine and iodine.

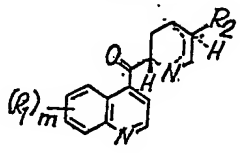
The process for preparing the above quinoline derivatives of formulae I and II, of

their antipodes or racemates and acid addition salts thereof, is characterized in that compounds of the general formulae



V

and



VI

wherein R_1, R_2 and m have the above meanings,

their antipodes or racemates thereof, are treated with a stereoselective reducing agent, that, if desired, in a so obtained compound wherein R_2 is a lower alkenyl group, this alkenyl group is reduced to a lower alkyl group and that, if desired, so obtained bases are converted into acid addition salts.

The compounds of the above formulae I and II are new compounds, except those wherein $(R_1)_m$ is hydrogen or a hydroxy or a lower alkoxy group in position 6′ and R_2 is vinyl or ethyl. The novel compounds are also a subject of the present invention. The compounds of the above formulae I and II, are useful antimalarial and antiarrhythmic agents.

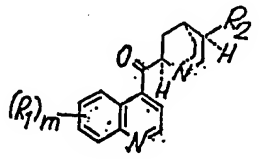
The conversion of the 4-[5(R)-alkyl(or alkenyl)-4(S)-quinuclidin-2(R)-ylcarbonyl]quinolines of formula V, antipodes or racemates thereof to α(S) - [5(R) - alkyl (or alkenyl) - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanols of formula I, antipodes or racemates thereof, respectively, is carried out utilizing a stereoselective reducing agent, for example, a diloweralkylaluminium hydride, such as diisobutylaluminium hydride. The reduction is suitably carried out at room temperature; however, temperatures above or below room temperature may be employed. It is preferred to employ a temperature between 20°C and 50°C. The reduction can be conveniently conducted in the presence of an inert organic solvent, for example, a hydrocarbon such as benzene, toluene, xylene, or an ether such as diethylether or tetrahydrofuran dioxane.

The conversion of the 4 - [5(R) - alkyl(or alkenyl) - 4(S) - quinuclidin - 2(S)-ylcarbonyl]quinolines of formula VI antipodes or racemates thereof, to the α(R)-[5(R) - alkyl(or alkenyl) - 4(S) - quinuclidin - 2(S) - yl] - 4 - quinolinemethanols of formula II, antipodes or racemates thereof, respectively, is carried out according to the procedures described for the conversion of the compounds of formula V.

The reduction of the compounds wherein R_2 is a lower alkenyl group, to compounds wherein R_2 is a lower alkyl group can be carried out with diimine in a manner known *per se*.

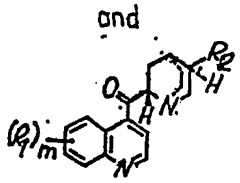
Preferably the starting material used for the above mentioned process for preparing derivatives of the formulae I and II is a compound of formula V or VI in which R_2 is vinyl or ethyl and $(R_1)_m$ is hydrogen, lower alkyl, methoxy or halogen in position 6′ or 7′ or in positions 6′ and 7′ or antipodes or racemates thereof.

In a further aspect, the present invention is concerned with a process for the manufacture of quinoline derivatives of the general formulae



V

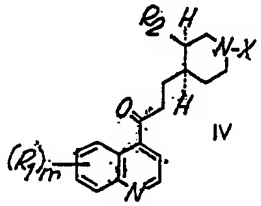
and



VI

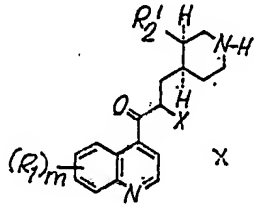
wherein R_1 is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or methylenedioxy, R_2 is lower alkyl or lower alkenyl and m is the integer 1 or 2, with the proviso that when R_1 is methylenedioxy m is the integer 1,
of their antipodes or racemates and acid addition salts thereof.

The process for preparing the above quinoline derivatives of formula V and VI, of their antipodes or racemates and acid addition salts thereof, is characterized in that a compound of the general formula



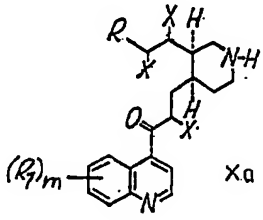
IV

wherein R_1, R_2 and m have the above meanings and X is halogen, with the proviso that when $(R_1)_m$ is hydrogen or a methoxy group in position 6' and R_2 is vinyl or ethyl, X is other than bromine,
or antipodes or racemates thereof, or a compound of the general formula



X

wherein R_1, X and m have the above meanings and R'_2 is lower alkyl,
or antipodes or racemates thereof, or a compound of the general formula



Xa

wherein R_1, X and m have the above meanings and R is hydrogen or alkyl with 1 to 5 carbon atoms,
or antipodes or racemates thereof, is cyclized by means of a cyclization agent, that in case a compound of formula Xa, antipodes or racemates thereof is used as starting material, the cyclization product is dehalogenated and that, if desired, the so obtained bases are converted into acid addition salts.

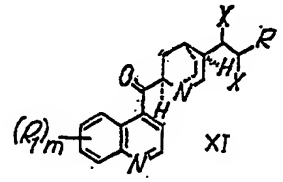
The compounds of the above formulae V and VI are new compounds, except wherein $(R_1)_m$ is hydrogen, or a hydroxy or a methoxy group in position 6′ and R_2 is vinyl or ethyl. The novel compounds are also a subject of the present invention.

The compounds of the above formulae V and VI are useful antimalarial and antiarrhythmic agents.

Preferably, there is used as starting material for manufacturing a compound of the general formulae V or VI a compound of formula IV, in which X is chlorine, R_2 is vinyl or ethyl and $(R_1)_m$ is hydrogen, halogen or methoxy in position 6′ or 7′ or positions 6′ and 7′.

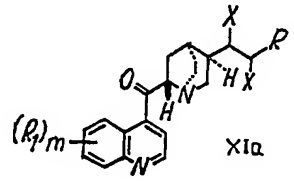
The 4 - [3 - (1 - halogen - 3(R) - alkyl(or alkenyl) - piperid - 4(R) - yl) - 1-oxopropyl]quinolines of formula IV antipodes or racemates thereof, are converted to the corresponding epimeric 4 - [5(R) - alkyl(or alkenyl) - 4(S) - quinuclidin - 2(R)-ylcarbonyl] - quinolines of formula V, antipodes or racemates thereof, and 4 - [5(R)-alkyl(or alkenyl) - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinolines of formula VI, antipodes or racemates thereof, under acidic or basic conditions, utilizing a cyclizing agent. Exemplary of such agents are inorganic or organic acids such as mineral acids, for example, phosphoric acid and sulfuric acid, strong alkanoic acids, for example trichloracetic acid and trifluoroacetic acid, or mixtures thereof, for example, acetic/sulfuric acid, or organic bases such as an alkali or alkaline earth metal alkoxide, for example, sodium ethoxide in ethanol and sodium methoxide in methanol. The reaction is conveniently carried out at room temperature or above, preferably at a temperature between 20°C and 50°C. Moreover, the cyclization can be suitably carried out in the presence of an inert solvent such as a hydrocarbon, e.g. benzene, toluene, xylene, a halogenated hydrocarbon, e.g. dichloromethane or chloroform or an ether e.g. diethylether or dioxane. As mentioned above, the cyclization yields a mixture of the epimeric compounds of formulae V and VI, which can be reacted further as such or can be separated into the respective epimers utilizing known methods, such as crystallization, and such epimer reacted separately.

The cyclisation of the halogenated compounds of formulae X and Xa, antipodes or racemates thereof, to the corresponding compounds of formulae V and VI, antipodes or racemates thereof, is effected according to the procedure described for the cyclization of the compounds of formula IV. When a compound of formula Xa, antipodes or racemates thereof is used as starting material, the cyclization products of the general formulae



XI

and

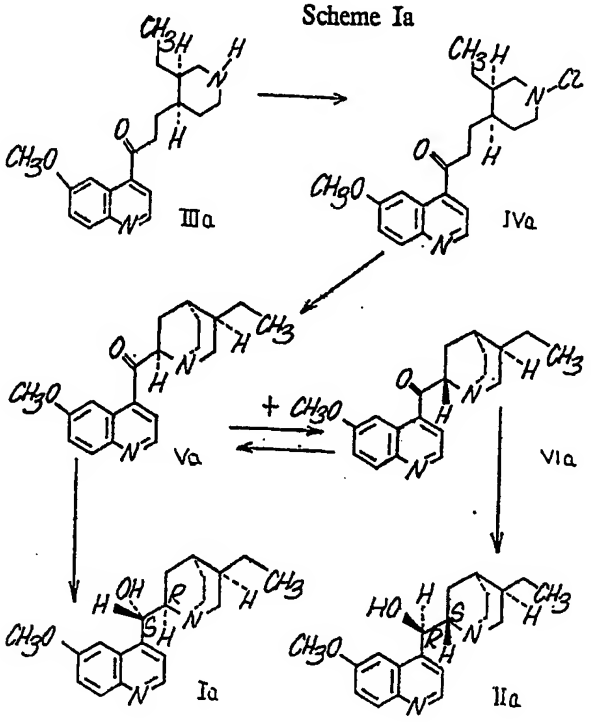


XIa

wherein R_1, m, R and X have the same meanings as in formula Xa,
antipodes or racemates thereof, are further dehalogenated to the compounds of formulae V and VI in which R_2 is a lower alkenyl group, antipodes or racemates thereof. The dehalogenation can be effected with, for example, sodium iodide.

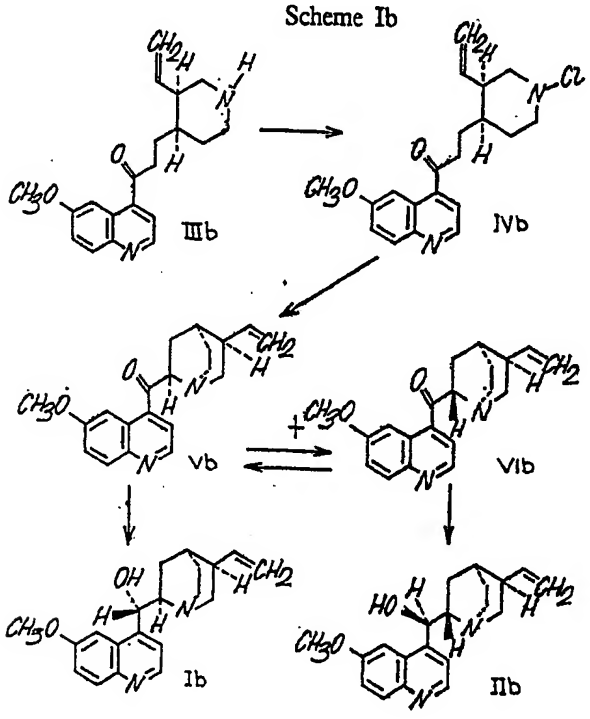
The following reaction schemes Ia and Ib represent preferred embodiments of the process of the present invention:

Scheme Ia



Reaction Scheme Ia represents the preparation of dihydroquinidine and dihydroquinine, and is carried out utilizing the reaction conditions as previously described. In Reaction Scheme Ia, dihydroquinotoxine of the formula IIIa antipode or racemate thereof, is converted to N-chlorodihydroquinotoxine of formula Iva, antipode or racemate thereof. The N-chlorodihydroquinotoxine of formula IVa, antipode or racemate thereof is converted to the epimeric dihydroquinidinone of formula Va antipode or racemate thereof and dihydroquininone of formula VIa antipode or racemate thereof which, are in turn converted to dihydroquinidine of formula Ia, antipode or racemate thereof and dihydroquinine of formula IIa, antipode or racemate thereof, respectively.

Scheme Ib



Reaction Scheme Ib represents the preparation of quinidine and quinine, antipodes or racemates thereof and is carried out utilizing the reaction conditions as previously described. In Reaction Scheme Ib, quinotoxine of formula IIIb antipode or racemate thereof is converted to N-chloro-quinotoxine of formula IVb, antipode or racemate thereof. The N-chloro-quinotoxine of formula IVb, antipode or racemate thereof, is converted to quinidinone of formula Vb, antipode or racemate thereof, and quininone of formula VIb, antipode or racemate thereof, which are in turn converted to quinidine of formula Ib, antipode or racemate thereof and quinine of formula IIb, antipode or racemate thereof, respectively.

As previously mentioned the compounds of the formulae I and II are new compounds, except those wherein $(R_1)_m$ is hydrogen or a hydroxy or a lower alkoxy group in position 6' and R_2 is vinyl or ethyl, and the compounds of the formulae V and VI are new except wherein $(R_1)_m$ is hydrogen or a hydroxy or a methoxy group in position 6' and R_2 is vinyl or ethyl.

Exemplary of the new compounds of formulae I and II are:

6 - Methoxy - α(S) - [5(R) - propyl - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanol, antipode and racemic analog;

6 - Methoxy - α(R) - [5(R) - allyl - 4(S) - quinuclidin - 2(S) - yl] - 4 - quinolinemethanol, antipode and racemic analog;

7 - Methoxy - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanol [hereinafter referred to as 7'-methoxy-dihydrocinchonine], antipode and racemic analog;

7 - Methoxy - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4 - quinolinemethanol [hereinafter referred to as 7'-methoxy-dihydrocinchonidine], antipode and racemic analog;

6,7 - Dimethoxy - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4-quinolinemethanol [hereinafter referred to as 6',7'-dimethoxydihydrocinchonine], its antipode and racemic analog;

6,7 - Dimethoxy - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4-quinolinemethanol [hereinafter referred to as 6',7'-dimethoxydihydrocinchonidine], its antipode and racemic analog;

6 - methyl - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanoil [hereinafter referred to as 6'-methyl-dihydrocinchonine] its antipode and racemic analog;

6 - methyl - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4 - quinolinemethanol [hereinafter referred to as 6'-methyl-dihydrocinchonidine], its antipode and racemic analog;

6 - chloro - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanol [hereinafter referred to as 6'-chloro-dihydrocinchonine], its antipode and racemic analog;

6 - chloro - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4 - quinolinemethanol [hereinafter referred to as 6'-chloro-dihydrocinchonidine], its antipode and racemic analog;

7 - chloro - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanol [hereinafter referred to as 7'-chloro-dihydrocinchonine], its antipode and racemic analog;

7 - chloro - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4 - quinolinemethanol [hereinafter referred to as 7'-chloro-dihydrocinchonidine], its antipodes and racemic analog;

7 - chloro - α(S) - [5(R) - vinyl - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanol [hereinafter referred to as 7'-chloro-cinchonine], its antipode and racemic analog;

7 - chloro - α(R) - [5(R) - vinyl - 4(S) - quinuclidin - 2(S) - yl] - 4 - quinolinemethanol [hereinafter referred to as 7'-chloro-cinchonidine], its antipode and racemic analog.

Exemplary of the new compounds of formulae V and VI are:

7 - Methoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl]-quinoline [hereinafter referred to as 7'-methoxy-dihydrocinchoninone], its antipode and racemic analog;

7 - Methoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline [hereinafter referred to as 7'-methoxy-dihydrocinchonidinone], its antipode and racemic analog;

6,7 - Dimethoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl]-

quinoline [hereinafter referred to as 6′,7′-dimethoxy-dihydrocinchoninone], its antipode and racemic analog;

6,7 - Dimethoxy - 4[5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl]quinoline [hereinafter referred to as 6′,7′-dimethoxy-dihydrocinchonidinone], its antipode and racemic analog;

6 - methyl - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl - carbonyl]quinoline [hereinafter referred to as 6-methyl-dihydrocinchoninone], its antipode and racemic analog;

6 - methyl - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl - carbonyl]quinoline [hereinafter referred to as 6′-methyl-dihydrocinchonidinone], its antipode and racemic analog;

6 - chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl - carbonyl]quinoline [hereinafter referred to as 6′-chloro-dihydrocinchoninone], its antipode and racemic analog:

6 - chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl - carbonyl]quinoline [hereinafter referred to as 6′-chloro-dihydrocinchonidinone], its antipode and racemic analog.

7 - chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl - carbonyl]quinoline [hereinafter referred to as 7′-chloro-dihydrocinchoninone], its antipode and racemic analog;

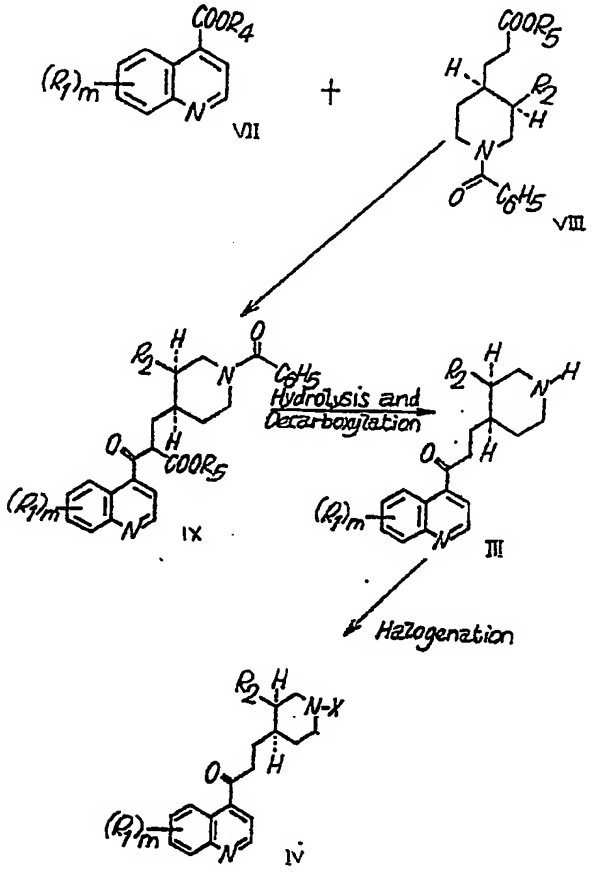
7 - chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl - carbonyl]quinoline [hereinafter referred to as 7′-chloro-dihydrocinchonidinone], its antipode and racemic analog.

7 - chloro - 4 - [5(R) - vinyl - 4(S) - quinuclidin - 2(R) - yl - carbonyl]quinoline [hereinafter referred to as 7′-chloro-cinchoninone] its antipode and racemic analog;

7 - chloro - 4 - [5(R) - vinyl - 4(S) - quinuclidin - 2(S) - yl - carbonyl]quinoline [hereinafter referred to as 7′-chloro-cinchonidinone], its antipode and racemic analog.

The starting materials of formulae IV, X and Xa, antipodes or racemates and acid addition salts thereof, which are new compounds, except those of formulae IV, X and Xa, wherein $(R_1)m$ is a methoxy group in position 6′, R_2 is vinyl or ethyl and X is bromine, can be manufacture according to the following reaction schemes II, IIa and IIb:

Scheme II



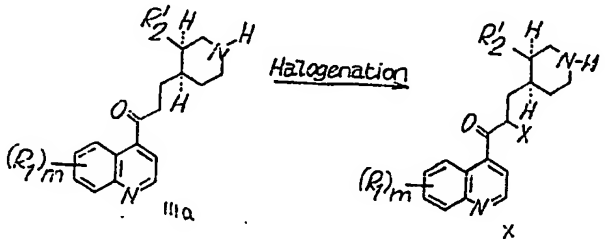
wherein R_1, m, and R_2 are as previously described, R_4 and R_5 are lower alkyl.

In Reaction Scheme II, the cinchoninic acid lower alkyl esters of Formula VII, which are known or are analogs of known compounds readily obtained by known procedures, are reacted in the presence of a base, for example, alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, and potassium tertiary butoxide, with the 3 - [1 - benzoyl - 3(R) - alkyl(or alkenyl) - 4(R) - piperidyl]propionic acid esters of Formula VIII, antipodes or racemates thereof, which are known compounds or are analogs of known compounds readily obtained by known procedures, or by the procedure hereinafter described in Scheme III, to yield the corresponding α - [1-benzoyl - 3(R) - alkyl(or alkenyl) - 4(R) - piperidyl - methyl] - β - oxo - 4 - quinolinepropionic acid esters of Formula IX, antipodes or racemates thereof. The reaction is conveniently conducted at reflux temperatures; however, lower temperatures may also be employed. An inert solvent, for example, ethers such as tetrahydrofuran and dioxan, may also be conveniently employed.

The conversion of the α - [1 - benzoyl - 3(R) - alkyl(or alkenyl) - 4(R) - piperidylmethyl] - β - oxo - 4 - quinolinepropionic acid esters of Formula IX to the corresponding 4 - [3 - (3(R) - alkyl(or alkenyl) - 4(R) - piperidyl) - 1 - oxopropyl]quinolines of Formula III, is effected utilizing a hydrolyzing agent, for example, an inorganic acid such as hydrochloric acid and sulfuric acid at reflux temperatures. Conveniently, temperatures below reflux may also be utilized.

The N-halogenation of the compounds of Formula III, antipodes or racemates thereof, to the corresponding N-halo compounds of Formula IV, antipodes or racemates thereof, is effected utilizing a halogenating agent such as hypobromous acid, sodium hypochlorite, N-chlorosuccinimide, N-bromosuccinimide or N-bromoacetamide in an inert organic solvent, for example, an ether such as tetrahydrofuran or dioxane; a chlorinated hydrocarbon such as methylene chloride, chloroform or carbon tetrachloride; or an alkanol such as methanol or ethanol.

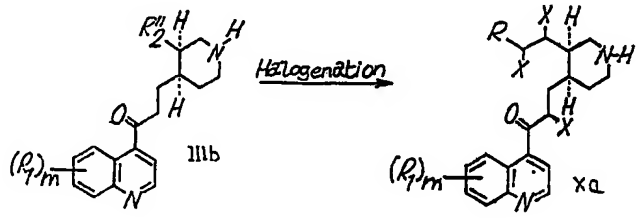
Scheme IIa



wherein R_1, m and X are as previously mentioned and R'_2 is lower alkyl.

In Reaction Scheme IIa, the C-halogenation of the compounds of Formula IIIa, antipodes or racemates thereof, to the corresponding compounds of Formula X, antipodes or racemates thereof, can be effected with a halogenating agent, for example, molecular halogen, such as chlorine or bromine in the presence of a hydrogen halide such as hydrogen chloride or hydrogen bromide in water, ether, acetic acid or other inert organic solvents.

Scheme IIb



wherein R_1, m and X are as previously mentioned and R is hydrogen or lower alkyl with 1 to 5 carbon atoms and R''_2 is lower alkenyl.

In Reaction Scheme IIb, the halogenation of the compounds of Formula IIIb, antipodes or racemates thereof, to the corresponding compounds of Formula Xa, antipodes or racemates thereof, is effected utilizing a halogenating agent, for example, molecular halogen, such as chlorine or bromine in the presence of a hydrogen halide, such as hydrogen chloride or hydrogen bromide in water, ether, acetic acid or other inert organic solvents.

From the above scheme IIa it is clear that the halogenation of compounds of formula IIIa to the compounds of formula X is only possible in case R'_2 in formula IIIa is lower alkyl. From scheme IIb it is clear that compounds of formula Xa are only obtained in case R''_2 in formula IIIb is lower alkenyl. Exemplary of the compounds of formulae IX, which are also novel compounds, except those wherein $(R_1)_m$ is methoxy in position 6′ and R_2 is vinyl or ethyl, III and IV are:

α - [1 - benzoyl - 3(R) - ethyl - 4(R) - piperidylmethyl] - β - oxo - β - (7-methoxy - 4 - quinolyl)propionic acid ethyl ester, its antipode or racemic analog;

α - [1 - benzoyl - 3(R) - ethyl - 4(R) - piperidylmethyl] - β - oxo - β - (6,7-dimethoxy - 4 - quinolyl)propionic acid ethyl ester; its antipode and racemic analog;

α - [1 - benzoyl - 3(R) - ethyl - 4(R) - piperidylmethyl] - β - oxo - β - (6-methyl - 4 - quinolyl)propionic acid ethyl ester, its antipode and racemic analog;

α - [1 - benzoyl - 3(R) - ethyl - 4(R) - piperidylmethyl] - β - oxo - β - (6-chloro - 4 - quinolyl)propionic acid ethyl ester, its antipode and racemic analog;

α - [1 - benzoyl - 3(R) - ethyl - 4(R) - piperidylmethyl] - β - oxo - β - (7-chloro - 4 - quinolyl)propionic acid ethyl ester, its antipode and racemic analog;

α - [1 - benzoyl - 3(R) - vinyl - 4(R) - piperidylmethyl] - β - oxo - β - (7-chloro - 4 - quinolyl)propionic acid ethyl ester, its antipode and racemic analog;

7 - Methoxy - 4 - [3 - (3(R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl] quinoline [hereinafter referred to as 7′-methoxy-dihydrocinchotoxine], its antipode and racemic analog;

6,7 - Dimethoxy - 4 - [3 - (3(R) - ethyl - 4(R) - piperidyl) - 1 - oxo - propyl] - quinoline [hereinafter referred to as 6′,7′-dimethoxy-dihydrocinchotoxine], its antipode and racemic analog;

6 - methyl - 4 - [3 - (3R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl] quinoline

[hereinafter referred to as 6′-methyl-dihydrocinchotoxine] its antipode and racemic analog;

6 - chloro - 4 - [3 - (3R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as 6′-chloro-dihydrocinchotoxine], its antipode and racemic analog;

7 - chloro - 4 - [3 - (3R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as 7′-chloro-dihydrocinchotoxine], its antipode and racemic analog;

7 - chloro - 4 - [3 - (3R) - vinyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as 7′-chloro-cinchotoxine], its antipode and racemic analog.

6 - methoxy - 4 - [3 - (1 - chloro - 3(R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as N-chloro-dihydroquinotoxine] its antipode and racemic analog;

7 - methoxy - 4 - [3 - (1 - chloro - 3(R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as N-chloro-7′-methoxy-dihydrocinchotoxine] its antipode and racemic analog;

6 - methoxy - 4 - [3 - (1 - chloro - 3(R) - vinyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as N-chloro-quinotoxine]; its antipode and racemic analog;

6,7 - dimethoxy - 4 - [3 - (1 - chloro - 3(R) - ethyl - 4(R) - piperidyl) - 1-oxopropyl]quinoline [hereinafter referred to as N-chloro-6′,7′-dimethoxy-dihydrocinchotoxine], its antipode and racemic analog;

6 - methyl - 4 - [3 - (1 - chloro - 3(R) - ethyl - 4(R) - piperidyl) - 1 -oxopropyl]quinoline [hereinafter referred to as N-chloro-6′-methyl-dihydrocinchotoxine], its antipode and racemic analog;

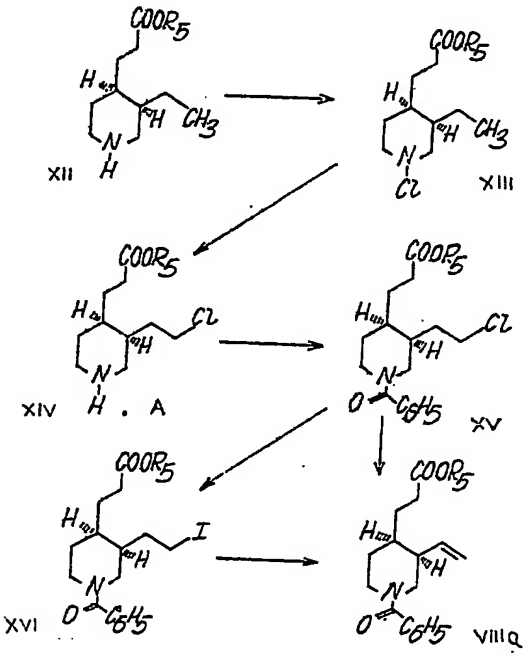
6 - chloro - 4 - [3 - (1 - chloro - 3(R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as N-chloro-6′-chloro-dihydrocinchotozine], its antipode and racemic analog;

7 - chloro - 4 - [3 - (1 - chloro - 3(R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as N-chloro-7′-chloro-dihydroxycinchotoxine], its antipode and racemic analog;

7 - chloro - 4 - [3 - (1 - chloro - 3(R) - vinyl - 4(R) - piperidyl) - 1 - oxopropyl]quinoline [hereinafter referred to as N-chloro-7′-chloro-cinchotoxine], its antipode and racemic analog;

The preparation of the 3 - [1 - benzoyl - 3(R) - vinyl - 4(R) - piperidinepropionic acid esters of Formula VIIIa, antipodes or racemates thereof, can be carried out as set forth in Reaction Scheme III.

Scheme III



wherein R_3 is as previously described, and A is an inorganic acid such as sulfuric acid and phosphoric acid, or organic acids, for example, lower alkanoic acids such as acetic acid, halogenated lower alkanoic acids such as trifluoroacetic acid and trichloroacetic acid.

In Reaction Scheme III, the 3-[3(R)-ethyl-4(R)-piperidine]propionic acid esters of Formula XII, antipodes or racemates thereof, which are known compounds, are converted to the corresponding 3 - [1 - chloro - 3(R) - ethyl - 4(R) - piperidine]propionic acid esters of Formula XIII, antipodes or racemates thereof, by utilizing a chlorinating agent, for example, N-chloro-succinimide, N-chloro-acetamide, alkali metal hypochlorite such as sodium hypochlorite. The reaction is conducted in an inert organic solvent, for example, a hydrocarbon such as benzene, toluene, xylene, a halogenated hydrocarbon such as dichloromethane, an alkanol such as methanol and ethanol, an ether such as diethylether, dioxane and tetrahydrofuran. The reaction temperature is not critical; however, preferably, it is in the range of −20° to +50°C, most preferably it is in the range of 0°C and room temperature.

The conversion of the compounds of Formula XIII, their antipodes or racemates, to the corresponding 3 - [3(R) - (2 - chloroethyl) - 4(R) - piperidine]propionic acid ester salts of the Formula XIV, antipodes or racemates thereof, is effected by irridiation with ultraviolet light source, such as a 200W-Hanovia (Registered Trade Mark) high pressure mercury lamp in an acid. The reaction temperature is not critical; however, preferably, it is in the range of 0°C to room temperature.

The conversion of the compounds of Formula XIV, antipodes or racemates thereof, to corresponding 3 - [1 - benzoyl - 3(R) - (2 - chloroethyl) - 4(R) - piperidine]propionic acid esters of Formula XV, antipodes or racemates thereof, is effected utilizing a benzoyl halide such as benzoyl bromide or chloride, in an inert organic solvent, for example, a hydrocarbon such as benzene and toluene, a halogenated hydrocarbon such as dichloromethane and chloroform, or ethers such as diethyl ethers, tetrahydrofuran and dioxane. The pH of the reaction mixture is maintained between 6 to 9 utilizing, for example, alkali metal carbonates such as sodium or potassium carbonate. The reaction temperature is not critical; however, preferably it is in the range of 0°C and room temperature.

The conversion of the compounds of Formula XV, antipodes or racemates thereof, to the corresponding 3 - [1 - benzoyl - 3(R) - (2 - iodoethyl) - 4(R) - piperidine]-propionic acid esters of the Formula XVI, antipodes or racemates thereof, is effected utilizing an alkali metal iodide in an inert organic solvent, for example, dimethylsulfoxide, dimethylformamide, acetonitrile, alkanols such as methanol and ethanol, or ketones such as acetone and methylethylketone. The temperature is not critical; however, preferably it is in the range of 0°C and the reflux of the reaction mixture.

The conversion of the compounds of Formula XVI, antipodes or racemates thereof, to the corresponding 3 - [1 - benzoyl - 3(R) - vinyl - 4(R) - piperidine]propionic acid esters of the Formula VIIIa, antipodes or racemates thereof, is effected utilizing an organic base, for example a tertiary organic amine such as pyridine, β-collidine and dimethylformamide. Advantageously, an inorganic salt, for example, lithium bromide, lithium chloride, lithium carbonate, silver fluoride and silver carbonate, may be utilized in the reaction. The reaction temperature is not critical; however, preferably it is in the range of room temperature and the reflux temperature of the reaction mixture.

The conversion of the compounds of Formula XV, antipodes or racemates thereof, to the corresponding 3 - [1 - benzoyl - 3(R) - vinyl - 4(R) - piperidine]propionic acid esters of the Formula VIIIa, antipodes or racemates thereof, is effected by pyrolysis, at a temperature between 100°C and 350°C, preferably at a temperature in the range of 150°C and 250°C. The reaction can be conducted at atmospheric pressure; however, preferably is conducted at reduced pressure, for example, in the range of 0.1 mm/Hg to 0.01 mm/Hg.

The compounds provided by the invention are bases. They can be converted into acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and with organic acids such as acetic acid, tartaric acid, maleic acid, fumaric acid, citric acid and oxalic acid.

The compounds of formulae I, II, V and VI and their pharmaceutically acceptable acid addition salts possess antimalarial and antiarrhythmic properties and are therefore useful as antimalarial and antiarrhythmic agents. Their pharmacologically useful antiarrhythmic activity is demonstrated in warm-blooded animals utilizing standard procedures, for example, the test compound is administered to prepared mongrel dogs. The chest cavity of the experimental animal previously anesthetized using a combination of sodium barbitol, 300 mg/kg and pentobarbitol, 15 mg/kg, i.v.,

is opened up through the third right interspace under artificial respiration and the pericardium is cut and sutured to the wall of the thorax so as to maintain the heart in a pericardial cradle throughout the course of the test procedure. Arterial pressure is monitored by inserting a polyethylene cannula into the aorta via the left carotid artery and is measured with an appropriate Statham pressure transducer. During the course of the experiment, electrical activity of the heart is viewed both on an oscilloscope and recorded on a Sanborn polyviso using standard ECG lead II. The heart is also observed visually. The antiarrhythmic assay of the test drug is undertaken using a modification of the method of Scherf and Chick, Circulation, *3, 764—769* (1951). A dripping of 1 percent solution of acetylcholine is applied to the sinus node and the atrium is irritated by pinching with a pair of forceps. This procedure produces a continuous atrial arrhythmia which mostly consists of atrial fibrillation. Since hypokalemia produces a susceptibility to atrial fibrillation (Leveque, Arch. Int. Pharmacodyn, *149,* 297—307, 1964), 2 units/kg of insulin is administered 30 minutes before the start of the acetylcholine drip. Once atrial fibrillation is established, there is a ten-minute waiting period before the test drug is administered. The test drugs are administered intravenously at the rate of 1 mg/kg/minute until normal sinus rhythm appears or until 30 mg/kg/minute of drug is administered.

When racemic 7′-methoxy-dihydrocinchonidinone is utilized as the test substance at a dosage of about 4.4 mg/kg, i.v., an antifibrillatory effect is observed for more than 60 minutes.

The pharmacologically useful antimalarial activity of the aforementioned compounds is demonstrated in warm-blooded animals using standard procedures, for example, the test substance is administered to albino mice in variable amounts. Albino mice are inoculated with about 10 million red cells infected with *P. Bergei.* Treatment is started on the first day after inoculation, and the drug is administered "*per os*" during 4 consecutive days. On the seventh day of infection, smears are made, stained with giemsa and microscopically examined for *P. Bergei.*

When racemic 7′-methoxy-dihydrocinchonidine dihydrochloride and racemic 7′-methoxy-dihydrocinchonice dihydrochloride are utilized as the test substance at dosages in the range of 125 mg/kg to about 250 mg/kg, the microscopical examination of the blood smears is free of *P. Berghei* (negative). The compounds of formulas I, II, V and VI and the pharmaceutically acceptable acid addition salts have effects quantitatively similar, for example, to those of quinine and quinidine of known therapeutic uses and properties. Thus, the compounds of the invention demonstrate a pattern of activity associated with antimalarials and antiarrhythmics of known efficacy and safety.

The novel compounds of formulas I, II, V and VI form acid addition salts and such salts are also within the scope of this invention. Thus, the aforementioned compounds from pharmaceutically acceptable addition salts with, for example, both pharmaceutically acceptable organic and inorganic acids, such as acetic acid, succinic acid, formic acid, methanesulfonic acid, *p*-toluene-sulfonic acid, hydrochloric acid, nitric acid, phosphoric acid and sulfuric acid.

The present invention also provides a pharmaceutical preparation comprising a novel quinoline derivative of the general formula I or II, an antipode, racemate or acid addition salt thereof in association with a compatible pharmaceutical carrier.

Additionally the invention provides a pharmaceutical preparation comprising a novel quinoline derivative of the general formula V or VI, an antipode, racemate or acid addition salt thereof in association with a compatible pharmaceutical carrier.

The novel products of the invention can be incorporated into standard pharmaceutical dosage forms, for example, they are useful for oral of parenteral application with the usual pharmaceutical adjuvants materials, e.g., organic or inorganic inert carrier materials such as water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums and polyalkylene glycols. The pharmaceutical preparations can be employed in a solid form, e.g., as tablets, troches, suppositories, capsules, or in liquid form, e.g., as solutions, suspensions or emulsions. The pharmaceutical adjuvant material can include preservatives, stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers. They can also contain other therapeutically active materials.

Furthermore, the novel compounds of the formulae I and II can be utilized as flavoring agents in beverages in the same manner as quinine is now used for this purpose.

The quantity of active medicament which is present in any of the above-described dosage forms in variable. The frequency with which any such dosage form will be

administered will vary, depending upon the quantity of active medicament present therein and the needs and requirements of the pharmacological situation.

Due to the possible different spatial arrangements of their atoms, it is to be understood that the compounds of this invention may be obtained in more than one possible stereo-isomeric form. The novel compounds, as described and claimed, are intended to embrace all such isomeric forms. Accordingly, the examples included herein are to be understood as illustrative of particular mixtures of isomers or single isomers and not as limitations upon the scope of the invention. All temperatures are in degrees centigrade, unless otherwise mentioned. Examples 4, 5, 19, 21a, 22—28, 29a and 29d relate to the preparation of intermediate compounds.

EXAMPLE 1

Preparation of Dihydroquinidinone

To a solution containing 1.5 g. of dihydroquinotoxine in 120 ml of methylene chloride were added 2.5 ml. of 17% aqueous NaOCl solution and the mixture was stirred for 16 hours at 20°, under nitrogen. The organic phase was separated, washed once with water, dried over anhydrous sodium sulfate, and evaporated. The crude N-chloro-dihydroquinotoxine (1.65 g) was dissolved in 10 ml of methylene chloride and added dropwise to 80 ml of 100% phosphoric acid which was stirrred vigorously; the viscous mixture was stirred at 20° for 4 hours. The mixture was cooled and made alkaline to a pH≈10 with 6N aqueous sodium hydroxide; the alkaline aqueous phase was extracted thoroughly with chloroform, which was dried over anhydrous sodium sulfate, and evaporated to dryness. The crude product (1.49 g) was chromatographed on a column of 50 g of neutral alumina, activity II; elution with methylene chloride yielded 1.1 g (73%) of an amorphous mixture of dihydroquinidinone which was crystallized from ethanol to yield 930 mg of dihydroquinidinone having a melting point of 102—104° after recrystallization from ether; $[\alpha]_D^{25}+71°$ (c 1.1, ethanol; after equilibration in ethanolic solution for 18 hours at 20°).

EXAMPLE 2

Preparation of Racemic dihydroquininone and racemic dihydroquinidinone from racemic dihydroquinotoxine

To a solution containing 14.8 g of racemic dihydroquinotoxine in 100 ml of chloroform were added 26 ml of 17% aqueous sodium hypochlorite solution, and the mixture was agitated under nitrogen at 20° for 16 hours. The aqueous phase was separated and washed with methylene chloride. The organic phase were combined, washed with water, dried over anhydrous sodium sulfate and evaporated to dryness.

The crude racemic N-chloro-dihydroquinotoxine (about 15 g) was dissolved in about 20 ml of methylene chloride and the concentrated solution was added dropwise to 120 ml of 100% phosphoric acid which was cooled in an ice-bath and vigorously stirred for 4 hours; the cooled solution was made alkaline with 6*N* aqueous sodium hydroxide and extracted thoroughly with ether. The etheral phase was dried over anhydrous potassium carbonate and evaporated to dryness.

The crude product (14 g) was chromatographed on 500 g of alumina, activity II. Elution with methylene chloride containing 0 to 1% of methanol yielded 10.1 g of pure, crystalline mixture of racemic dihydroquininone and racemic dihydroquinidinone (68% yield from dihydroquinotoxine). Crystallization from petroleum ether yielded 8.09 g of crystals in three crops. The first crop having a melting point of 89—95° was recrystallized four times from petroleum ether to yield racemic dihydroquininone having a melting point of 100—104°.

Recrystallization of the third crop, having a melting point of 80—82°, from petroleum ether yielded about a 1:1 mixture of racemic dihydroquininone and racemic dihydroquinidinone having a melting point of 80—83°.

EXAMPLE 3

Preparation of Quinidinone from Quinotoxine

To a solution containing 1.804 g of quinotoxine in 35 ml of methylene chloride were added 6.4 ml of about a 17% aqueous sodium hypochlorite solution, and the mixture was stirred under nitrogen for 2 1/2 hours at 20°. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The crude N-chloroquinotoxine (1.927 g) was dissolved in about 6 ml of methylene chloride-acetic acid 4:1 and added dropwise with stirring to 10 ml of 99.5% phosphoric acid. The resulting viscous mixture was stirred at 0—20° for 2 hours. The reaction mixture was poured into 50 ml of water. The aqueous phase was made alkaline with 6*N* sodium hydroxide and the temperature was allowed to rise to about

40°. After 10 minutes, the aqueous alkaline phase was extracted thoroughly with methylene chloride; the organic phase was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The crude product (1.714 g) was chromatographed through 17 g of neutral alumina, activity II; elution with methylene chloride yielded 1.178 g (66%) of a mixture of quinidinone and quininone. Crystallization from ether yielded 915 mg (51%) of quinidinone which after recrystallization from ether had a melting point of 98—101°; $[\alpha]_D^{25}+72.6°$ (c 0.99, ethanol; after equilibration in ethanolic solution for 18 hours at 20°).

EXAMPLE 4

Preparation of Racemic 7′-Methoxy-dihydrocinchotoxine from *cis*-3-(1-benzoyl-3-ethyl-4-piperidine)propionic acid ethyl ester and 7-methoxy-4-carbethoxy-quinoline

A solution containing 25.4 g of *cis*-3-(1-benzoyl-3-ethyl-4-piperidine)propionic acid ethyl ester in 250 ml of dry tetrahydrofuran was added dropwise (30 min.) to a gently refluxing mixture of 26.9 g of potassium t-butoxide and 25.8 g of 7-methoxy-4-carbethoxyquinoline in 400 ml. of dry tetrahydrofuran, in an atmosphere of dry nitrogen. The mixture was heated under gentle reflux for two hours, and the solvent was removed under reduced pressure. The residue was dissolved in 300 ml of 0.5*N* sodium hydroxide, and was washed with benzene. The alkaline aqueous phase containing α - *cis* - (1 - benzoyl - 3 - ethyl - 4 - piperidylmethyl) - β - oxo - β - (7-methoxy - 4 - quinolyl)propionicacid ethyl ester was acidified so that a 6*N* aqueous hydrochloric acid solution was obtained, and the solution was heated under reflux for 21 hours. The cooled reaction mixture was made alkaline with 6*N* sodium hydroxide, and extracted thoroughly with ether. The ethereal extracts were dried over anhydrous potassium carbonate and concentrated to dryness.

The crude product (21.0 g) was dissolved in a small volume of acetone and added to a solution containing 14.5 g of dibenzoyl-d-tartaric acid in acetone. The precipitate was separated by filtration, the free bases of the mother liquors were purified by preparative tlc to yield racemic 7′-methoxy-dihydrocinchotoxine. A sample of the neutral dibenzoyl-d-tartrate was recrystallized from methanol and had a melting point of 174—175.5°. The free base *dl*-7′-methoxy-dihydrocinchotoxine was obtained as a yellow oil.

EXAMPLE 5

Preparation of 7′-Methoxy-dihydrocinchotoxine from N-benzoylhomocincholoipone ethyl ester and 7-methoxy-4-carbethoxy quinoline

A solution containing 4.14 g of N-benzoylhomocincholoipone ethyl ester in 40 ml of dry tetrahydrofuran was added dropwise (20 min.) to a gently refluxing mixture of 4.98 g of potassium t-butoxide and 4.74 g of 7-methoxy-4-carbethoxyquinoline in 90 ml of dry tetrahydrofuran in an atmosphere of dry nitrogen. The mixture was heated under gentle reflux for three hours, then the solvent was removed by distillation under vacuum, and the cooled residue dissolved in 100 ml. of 0.5*N* sodium hydroxide. The alkaline phase was washed with benzene and the benzene phases washed with 0.5*N* sodium hydroxide. The combined aqueous phases containing α-[1 - benzoyl - 3(R) - ethyl - 4(R) - piperidylmethyl] - β - oxo - β - (7 - methoxy - 4-quinolyl)propionic acid ethyl ester were acidified so that a 6*N* hydrochloric acid solution was obtained, and then heated under gentle reflux for 17 hours. The cooled reaction mixture was made alkaline with 6*N* sodium hydroxide and thoroughly extracted with ether. The etheral extracts were dried over anhydrous potassium carbonate and evaporated to dryness. The crude product (3.30 g) was dissolved in a small volume of acetone, and 1.7 g of dibenzoyl-*d*-tartaric acid as a concentrated solution in acetone was added. Crystallization yielded 4.11 g (54%) of 7′-methoxy-dihydrocinchotoxine as its neutral dibenzoyl-*d*-tartrate; having a melting point of 177—179° after recrystallization from chloroform-methanol; $[\alpha]_D^{26}-39.6°$ [c 0.5, ethanol-chloroform (1:2)].

EXAMPLE 6

Preparation of 7′-methoxy-dihydrocinchoninone and 7′-methoxy-dihydrocinchonidinone from 7′-methoxy-dihydrocinchotoxine

To a solution containing 2.65 g of 7′-methoxy-dihydrocinchotoxine in 100 ml of chloroform were added 5 ml of about a 17% aqueous sodium hypochlorite solution. The resulting mixture was stirred at 20° for 16 hours. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate and evaporated. The crude N-chloro-7′-methoxy-dihydrocinchotoxine was dissolved in a minimal amount of chloroform and added dropwise to 15 ml of 100% phosphoric acid with vigorous

stirring. The resulting viscous mixture was stirred at 20° for 4 hours. Thereafter, it was made alkaline, with 6*N* potassium hydroxide and the temperature of the alkaline phase was allowed to reach about 40°. After 10 minutes, the aqueous phase was extracted thoroughly with ether. The ethereal phase was dried over anhydrous potassium carbonate, and concentrated to dryness. The crude product (2.49 g) was chromatographed on a column of 75 g of neutral alumina, activity II; elution with methylene chloride yielded 1.49 g (56%) of a mixture of 7′-methoxy-dihydrocinchoninone and 7′-methoxy-dihydrocinchonidinone having a melting point of 103—108° after recrystallization from petroleum ether; and a specific rotation of $[\alpha]_D^{25}+16°$ (c 0.27, ethanol; after equilibration in ethanolic solution for 18 hours at 20°).

Example 7

Preparation of Racemic 7′-methoxy-dihydrocinchonidinone and racemic 7′-methoxy-dihydrocinchoninone from racemic 7′-methoxy-dihydrocinchotoxine

To a solution containing 20.6 g of racemic 7′-methoxy-dihydrocinchotoxine in 150 ml of chloroform were added 55 ml of about a 17% aqueous sodium hypochlorite solution, and the mixture was agitated for 16 hours at 20°. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The crude racemic N-chloro-7′-methoxy-dihydrocinchotoxine was dissolved in a minimum volume of chloroform and added dropwise to 150 ml of concentrated phosphoric acid at 20° with vigorous stirring. The resulting viscous mixture was stirred for 2 hours. The solution was cooled with ice, diluted with water, and made alkaline with 6N sodium hydroxide. During neutralization, the temperature was allowed to reach about 40°. After about 10 minutes, the alkaline aqueous phase was extracted thoroughly with ether and the etheral phase was dried over anhydrous potassium carbonate and evaporated to dryness. The crude, crystalline product (20.4 g) was dissolved in petroleum ether leaving an insoluble, tarry residue of 3.4 g. Crystallization from the same solvent yielded 9.49 g of racemic 7′-methoxy-dihydrocinchonidinone and 7.52 g of an amorphous mixture of racemic 7′-methoxy-dihydrocinchoninone and racemic 7′-methoxy-dihydrocinchonidinone (total yield 82%). After 2 recrystallizations from petroleum ether, racemic 7′-methoxy-dihydrocinchonidinone had a melting point of 115—118°.

Example 8

Preparation of Dihydroquinidine from dihydroquinidinone

To a solution containing 2.0 g of dihydroquinidinone in 150 ml of dry toluene, stirred at 20° in an atmosphere of dry nitrogen, were added dropwise 4.8 ml of a 25% solution of di-*iso*butyl aluminium hydride in toluene. As soon as all the ketone was consumed, the reaction was quenched by the addition of 3 ml of water-methanol (1 : 1). The aluminium hydroxide which precipitated was separated by filtration and was washed thoroughly with benzene and methanol. The combined filtrates were evaporated to dryness, Crystallization of the residue from ethanol yielded 1.90 g of dihydroquinidine (94% yield) in three crops which after recrystallization from ethanol had a melting point of 168—169° $[\alpha]_D^{22}+227.9°$ (c 0.896, ethanol).

Example 9

Preparation of Dihydroquinidine and dihydroquinine from a mixture of dihyroquinidinone and dihydroquininone

A solution containing 1.25 g of dihydroquinidinone in 50 ml of benzene containing 0.5 ml of methanol was maintained at 20° for 2 1/2 days under nitrogen. The solution was evaporated to complete dryness under vacuum, and the residue was redissolved in benzene and again evaporated to dryness. The resulting oily residue was dissolved in 50 ml of dry benzene, and 3 ml of a 25% solution of di-isobutyl aluminium hydride in toluene were added dropwise with stirring under an atmosphere of dry nitrogen. The reaction was quenched after about 30 minutes by adding 10 ml. of water-methanol (1 : 1), and the mixture was stirred vigorously for 30 minutes. The benzene layer was decanted. The aqueous aluminium suspension was washed several times with benzene and the combined benzene phases were dried over anhydrous magnesium sulfate and evaporated to dryness. The crude product (1.25 g of colorless foam) was a practically pure mixture of dihydroquinidine and dihydroquinine (about 1 : 1) as determined by thin layer chromatography; and a specific rotation $[\alpha]_D^{24.5}+62.2°$ (c 1.64, ethanol). Crystallization from ethanol yielded 490 mg of pure dihydroquinidine having a melting point of 167—169°.

EXAMPLE 10

Preparation of racemic dihydroquinine from racemic dihydroquininone

To a solution containing 1.0 g of racemic dihydroquininone in 100 ml of dry benzene were added dropwise 2.5 ml of a 25% solution of di-*iso*butyl aluminium hydride in toluene with stirring under an atmosphere of dry ntirogen. After about 30 minutes, the reaction was quenched by the addition of 2 ml of methanol-water (1:1). The alumina which precipitated was separated by filtration, washed thoroughly with methanol, and the filtrate was evaporated to dryness. Crystallization of the crude product (1.003 g) from acetone yielded 718 mg of racemic dihydroquinine as its monohydrate, which after recrystallization from acetone had a melting point of 174—177°.

EXAMPLE 11

Preparation of anhydrous *d,l*-dihydroquinine

d,l-Dihydroquinine monohydrate after repeated evaporation from a benzene solution yielded *d,l*-dihydroquinine having a melting point of 172—174°.

EXAMPLE 12

Preparation of Racemic dihydroquinine sulfate

A solution containing 5.253 g of *d,l*-dihydroquinine in 20 ml. of methanol and 16.1 ml of 1*N* aqueous sulfuric acid was cooled at 0°. The precipitated crystals were separated by filtration, washed with acetone and dried at 60°/50 mm for 20 hours. After additional drying at 80°/0.01 mm, *d,l*-dihydroquinine sulfate was obtained, which contained 0.5 mole of water and had a melting point of 210—213°.

EXAMPLE 13

Preparation of Racemic dihydroquinine and racemic dihydroquinidine from a mixture of racemic dihydroquininone and racemic dihydroquinidinone

The reduction of 5.06 g of crystalline mixture of racemic dihydroquininone and dihydroquinidinone (melting point of 76—89°) was carried out in dry benzene with di-*iso*butyl aluminium hydride according to the procedures described in Example 8. The methanol extracts (3.87 g) were crystallized from acetone to yield 3.14 g (61%) of racemic dihydroquinine monohydrate in three crops. The benzene extracts (1.54 g) were crystallized from a concentrated solution in ethanol to yield 579 mg. (11%) of racemic dihydroquinidine in four crops. Racemic dihydroquinidine: after recrystallization from ethanol had a melting point of 152—154.5°.

EXAMPLE 14

Preparation of Racemic dihydroquinidine sulfate

To 2.02 g of *d,l*-dihydroquinidine in 25 ml of absolute ethanol were first added 6.2 ml of 1*N* aqueous sulfuric acid, followed by 5 ml of water. The sulfate (2.03 g) crystallized after the volume was evaporated to 20 ml. After drying at 80°/0.01 mm for 70 hours, the *d,l*-dihydroquinidine contained 3/4 mole of water and had a melting point of 208—211°.

EXAMPLE 15

Preparation of Quinidine from quinidinone

To a solution containing 1.00 g of quinidinone in 40 ml of dry benzene were added dropwise 2.4 ml of a 25% solution of di-*iso*butyl aluminium hydride in toluene. After stirring at 20° under an atmosphere of dry nitrogen, 10 ml of water was added. The benzene layer was separated, dried over anhydrous magnesium sulfate, and evaporated to dryness. The crude, crystalline product (0.890 g) was recrystallized from ethanol to yield 0.646 g of crystalline quinidine having a melting point of 169—171°; $[\alpha]_D^{25}$ +264.3 (c 0.98 ethanol).

In the like manner, the following can be prepared: 7 - chloro - α(S) - [5(R)-vinyl - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanol which crystallized from ethanol-acetone has a melting point of 247—250°, $[\alpha]_D^{25}$ +196° (c 0.88, ethanol-methylene chloride 4:1); and 7 - chloro - α(R) - [5(R) - vinyl - 4(S)-quinuclidin 2(S) - yl] - 4 - quinoline - methanol which recrystallized from acetone-ether, has a melting point of 165—169°; $[\alpha]_D^{25}$ −67° (c 0.90, ethanol).

EXAMPLE 16

Preparation of 7′-Methoxy-dihydrocinchonine and 7′-methoxy-dihydrocinchonidine from a mixture of 7′-methoxy-dihydrocinchoninone and 7′-methoxy-dihydrocinchonidinone

To a solution containing 1.46 g of a mixture of 7′-methoxy-dihydrocinchoninone

and 7′-methoxy-dihydrocinchonidinone in 50 ml of dry benzene, stirred under an atmosphere of dry nitrogen at 20°, were added dropwise 3.75 ml of a 25% solution of di-*iso*butyl aluminium hydride in toluene. When all the ketone was consumed, 5 ml of 50% aqueous methanol were added. The alumina which precipitated was separated by filtration, and washed thoroughly with benzene. The combined filtrates were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was triturated with acetone, and crystallization yielded 7′-methoxy-dihydrocinchonine. After recrystallizations from chloroform-petroleum ether, 7′-methoxy-dihydrocinchonine had a melting point of 231—233°; $[\alpha]_D^{25}$ +169.5° (c 1.00, ethanol). From the mother liquors, 7′-methoxy-dihydrocinchonidine was obtained by fractional crystallization from acetone. After recrystallization, 7′-methoxy-dihydrocinchonidine had a melting point of 162—165°; $[\alpha]_D^{25}$ −80.3° (c 0.98, ethanol).

Example 17

Preparation of Racemic 7′-methoxy-dihydrocinchonidine from racemic 7′-methoxy-dihydrocinchonidinone

To a solution containing 2.32 g of racemic 7′-methoxy-dihydrocinchonidinone (melting point 112—116°) in 50 ml of dry benzene were added dropwise 6.5 ml of a 25% solution of di-*iso*butyl aluminium hydride in toluene at 20° under an atmosphere of dry nitrogen. After stirring for about 30 minutes at 20°, 8 ml of 50% aqueous methanol were added. The alumina which precipitated was separated by filtration and washed thoroughly with benzene. The filtrate was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was triturated with ether and 1.78 g of crystalline racemic 7′-methoxy-dihydrocinchonidine having a melting point of 155—157° were collected.

Example 18

Preparation of Racemic 7′-methoxy-dihydrocinchonine and racemic 7′-methoxy-dihydrocinchonidine from a mixture of racemic 7′-methoxy-dihydrocinchoninone and 7′-methoxy-dihydrocinchonidinone

To a solution containing 2.52 g of an amorphous mixture of racemic 7′-methoxy-dihydrocinchonidinone and racemic 7′-methoxy-dihydrocinchoninone in 50 ml of dry benzene, were added dropwise 7.2 ml of a 25% solution of di-*iso*butyl aluminium hydride in toluene at 20° under an atmosphere of dry nitrogen. After stirring for about 30 minutes at 20°, 8 ml of 50% aqueous methanol were added the alumina which precipitated was separated by filtration and washed thoroughly with benzene. The filtrate was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was triturated with acetone and 1.01 g of isomer, i.e. racemic 7′-methoxy-dihydrocinchonine, were separated. It had a melting point 217—219° after recrystallization from chloroform-acetone. From the mother liquors, 0.63 g (25%) of the lower melting racemic 7′-methoxy-dihydrocinchonidine was isolated.

Example 19

Preparation of 6′,7′-Dimethoxy-dihydrocinchotoxine from 6,7-dimethoxy-4-carbethoxy-quinoline and N-benzoylhomocincholoipone ethyl ester

A solution containing 3.28 g of N-benzoyl-homocincholoipone ethyl ester in 30 ml of dry tetrahydrofuran was added dropwise (30 min.) to a gently refluxing mixture of 3.13 g of 6,7-dimethoxy-4-carbethoxyquinoline and 3.40 g of potassium t-butoxide in 50 ml of dry tetrahydrofuran in an atmosphere of dry nitrogen. The mixture was heated under reflux for an additional two hours and then the solvent was removed by distillation under reduced pressure. The cooled residue was dissolved in 75 ml of 0.5N sodium hydroxide. The alkaline phase was washed with benzene and the benzene extracts were washed with 0.5N sodium hydroxide. The combined aqueous phase was acidified with concentrated hydrochloric acid, so that about 6N hydrochloric acid solution was obtained, and heated under gentle reflux for 24 hours. The cold reaction mixture was made alkaline with 6N sodium hydroxide and was thoroughly extracted with ether. The etheral extracts were dried over anhydrous potassium carbonate and evaporated to dryness. The crude product was dissolved in a small volume of acetone, and 0.805 g of dibenzoyl-*d*-tartaric acid was added as a concentrated solution in acetone. Crystallization yielded 1.63 g of 6′,7′-dimethoxy-dihydrocinchotoxin neutral dibenzoyl-*d*-tartrate having a melting point of 161.5—163.5°, after three recrystallizations from methylene chloride/acetone; $[\alpha]_D^{25}$ −37.7° [c 1.02, chloroform-ethanol (2:1)].

EXAMPLE 20

Mixture of 6',7'-Dimethoxy-dihydrochoninone and 6',7'-dimethoxy-dihydrocinchonidinone from 6',7'-dimethoxy-dihydrocinchotoxine

To a solution containing 1.42 g of 6',7'-dimethoxy-dihydrocinchotoxine in 50 ml of chloroform was added 3.5 ml of about 17% aqueous sodium hypochlorite, and the mixture was stirred at 20° for 90 minutes. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate and concentrated to a volume of 10 ml. The solution containing 6,7-dimethoxy-4[3-(1-chloro-3(R)-ethyl-4(R)-piperidyl)-1-oxopropyl]-quinoline was added dropwise to 10 ml of 100% phosphoric acid, and the viscous mixture was stirred at 20° for 5 hours. The mixture was diluted with water, made alkaline with 6N potassium hydroxide while allowing the alkaline phase to reach about 40°, and extracted thoroughly with ether. The etheral phase was dried over anhydrous potassium carbonate and concentrated to dryness. The crude product was purified on preparative talc plates [chloroform-triethylamine (9:1)], to yield 0.794. g of a pure, amorphous mixture (about 1:1) of 6',7'-dimethoxy-dihydrocinchoninone and 6',7'-dimethoxy-dihydrocinchonidinone.

EXAMPLE 21

6',7'-Dimethoxy-dihydrocinchonine and 6',7'-dimethoxy-dihydrocinchonidine from a mixture of 6',7'-dimethoxy-dihydrocinchoninone and 6',7'-dimethoxy-dihydrocinchonidinone

To a solution containing 0.745 g. of a mixture of 6',7'-dimethoxy-dihydrocinchoninone and 6',7'-dimethoxy-dihydrocinchonidinone in 20 ml of dry benzene, which was stirred in an atmosphere of dry nitrogen at 20°, were added dropwise 1.5 ml of 25% di-*iso*butyl aluminium hydride in toluene. After about 60 minutes 5 ml of water-methanol (2:3) mixture was added. The precipitated alumina was separated by filtration and washed thoroughly with benzene. The combined filtrates were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was separated by preparative tlc (chloroform-triethylamine-methanol=85:110:5) into the two isomers 6',7'-dimethoxy-dihydrocinchonine and 6',7'-dimethoxy-dihydrocinchonidine. The less polar 6',7'-dimethoxy-dihydrocinchonine was crystallized from ether; and had a melting point of 116—118° after several recrystallizations from acetone; $[\alpha]_D^{25}$+182.2° (c 0.95, ethanol). The more polar 6',7'-dimethoxy-cinchonidine could not be recrystallized; $[\alpha]_D^{25}$—87.3° (c 0.68, ethanol).

EXAMPLE 21a

Preparation of Racemic 6',7'-Dimethoxydihydrocinchotoxine from cis-3-(1-benzoyl-3-ethyl-4-piperidine)propionic acid ethyl ester and 6,7-Dimethoxy-4-carbethoxyquinoline

A solution containing 31.7 g. of *cis*-3-(1-benzoyl-3-ethyl-4-piperidine)propionic acid ethyl ester in 250 ml. of dry tetrahydrofuran was added dropwise (40 min.) to a refluxing mixture of 36.5 g. of 6,7-dimethoxy-4-carbethoxy-quinoline and 33.6 g. of potassium t-butoxide in 500 ml. of dry tetrahydrofuran under an atmosphere of dry nitrogen. The mixture was heated under reflux for two hours and the solvent was removed under reduced pressure. The cold residue was dissolved in 300 ml. of 0.5N soduim hydroxide and washed with four 60 ml. portions of benzene. The combined aqueous phases containing the β-ketoester were acidified with conc. HCl, whereby a 6N hydrochloric acid solution was obtained, and then heated under reflux for 24 hours. The reaction mixture was allowed to call, made alkaline with 6N sodium hydroxide and extracted with ether. The ethereal extracts were dried over anhydrous potassium carbonate and evaporated to dryness to give 14.5 g. (40%) of amorphous racemic 6',7'-dimethoxydihydrocinchotoxine.

EXAMPLE 21b

Preparation of Racemic 6',7'-Dimethoxydihydrocinchonidinone and Racemic 6',7'-Dimethoxydihydrocinchoninone from Racemic 6' 7'-Dimethoxydihydrocinchotoxine

To a solution containing 14.5 g. of racemic 6',7'-dimethoxydihydrocinchotoxine in 200 ml. of dichloromethane was added 25 ml. of about a 17% aqueous sodium hypochlorite, and the mixture was stirred vigorously for 60 min. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate, and evaporated to a volume of about 20 ml. This solution containing the chloramine was added dropwise to 60 ml. of 99.5% phosphoric acid. The cosolvent was evaporated and the viscous mixture stirred at 20° for 4 hours. The mixture was diluted with water and made alkaline with 6N sodium hydroxide. The alkaline phase was allowed to reach

about 40°, and was extracted with ether. The ethereal phase was dried over anhydrous potassium carbonate and concentrated to dryness. The product (12.8 g.) was absorbed on 100 g. of neutral alumina, activity II. Elution with benzene and dichloromethane yielded 9.2 g. (65%) of an amorphous mixture comprising racemic 6′,7′-dimethoxydihydrocinchonidinone and racemic 6′,7′-dimethoxydihydrocinchoninone.

EXAMPLE 21c

Preparation of Racemic 6′,7′-Dimethoxydihydrocinchonidine and Racemic 6′,7′-Dimethoxydihydrocinchonine from a mixture of racemic 6′,7′-Dimethoxydihydrocinchonidinone and Racemic 6′,7′-Dimethoxydihydrocinchoninone

To a solution containing 9.2 g. of a mixture of the racemic 6′,7′-dimethoxydihydrocinchonidinone and racemic 6′,7′-dimethoxydihydrocinchoninone in 200 ml. of dry benzene, which was stirred under an atmosphere of dry nitrogen at 20°, was added dropwise a 25% solution of di-*iso*butyl aluminum hydride in toluene. After the addition of 17.5 ml., the reaction was completed. The reaction was quenched by addition of 40 ml. of methanol-water (3:2). The precipitated alumina was separated by filtration and washed thoroughly with benzene. The filtrates were combined. The benzene layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness. The product was separated by preparative thin layer chromatography (silica gel GF_{254}; chloroform-triethylamine-methanol, 85:10:5). The less polar fraction yielded 4.4 g. of amorphous, racemic 6′,7′-dimethoxydihydrocinchonine.

For final purification, the base was converted to the racemic 6′,7′-dimethoxydihydrocinchonine dihydrochloride, which had a melting point of 221—225° (dec.) after recrystallization from methanol.

The more polar fraction (3.4 g.) containing racemic 6′,7′-dimethoxydihydrocinchonidine gave crystals from acetone having a melting point of 155—157°. Racemic 6′,7′-dimethoxydihydrocinchonidine dihydrochloride was obtained after recrystallization from methanol and had a melting point of 208—210° (dec.).

EXAMPLE 22

Rac. *cis*-3-[1-chloro-3-ethyl-4-piperidine]propionic acid ethyl ester

A. To a solution of 1.064 g of racemic *cis*-3-[3-ethyl-4-piperidine]propionic acid ethyl ester in 30 ml. of ether was added 30 ml. of a 16.9 percent aqueous solution of sodium hypochlorite. The mixture was shaken at room temperature. In intervals of 1 hour the aqueous layer was separated and fresh sodium hypochlorite solution (30 ml.) was added. After 4.5 hours, 100 ml. of benzene was added to the mixture. The organic layer was separated and washed successively with water (2×), 3N aqueous hydrochloric acid (3×) and water (3×). After drying over sodium sulfate and evaporating under reduced pressure 0.90 g. of liquid racemic *cis*-3-[1-chloro-3-ethyl-4-piperidine]propionic acid ethyl ester was obtained.

B. To a stirred suspension of 11 g. of N-chlorosuccinimide in 200 ml. of anhydrous ether was added in a nitrogen atmosphere a solution of 15 g. of racemic *cis*-3-[3-ethyl-4-piperidine]propionic acid ethyl ester in 100 ml. of anhydrous ether. After continued stirring for 1 hour at room temperature the mixture was successively washed with water (3×), 2.5N aqueous sulfuric acid (2×) and water. The ethereal solution was dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 18 g. of liquid racemic *cis*-3-[1-chloro-3-ethyl-4-piperidine]-propionic acid ethyl ester.

EXAMPLE 23

Rac. *cis*-3-[1-benzoyl-3-(2-chloroethyl)-4-piperidine]propionic acid ethyl ester

Eighteen grams of racemic *cis*-3-[1-chloro-3-ethyl-4-piperidine]propionic acid ethyl ester was dissolved in 150 ml. of trifluoroacetic acid at 0°. The resulting clear solution was transferred to a quartz flask, purged with dry nitrogen for 30 minutes and then irradiated at 10° with a 200W-Hanovia (Registered Trade Mark) high-pressure mercury lamp. At intervals, samples were removed and the reaction was continued until a negative starch-iodide test was obtained. After 5 hours, the solvent was removed at 35° under reduced pressure. Benzene was added to the residue and evaporated under reduced pressure. This procedure was reperated several times. To a stirred solution of 40 g. of the crude racemic *cis*-3-[3-(2-chloroethyl)-4-piperidine]propionic acid ethyl ester trifluoroacetate and 26 g. of benzoyl chloride in 400 ml. of benzene was added over a period of 2 hours a saturated aqueous solution of potassium carbonate until the pH reached 9. Stirring was continued for 1 hour. After the addition of 200 ml. of benzene, the mixture was washed successively with 6N aqueous sodium hydroxide (3×) water, 3N aqueous hydrochloric acid and water. The organic layer was sepa-

rated and dried over anhydrous sodium sulfate. Evaporation to dryness gave 30 g. oily material, which was chromatographed on 650 g. of silica gel with benzene:ethyl acetate (9:1) as the liquid phase to give 22.3 g. of 96.3 per cent pure of racemic *cis*-3-[1-benzoyl-3-(2-chloroethyl)-4-piperidine]propionic acid ethyl ester. Yield 87 per cent.

EXAMPLE 24

Rac. *cis*-3-[1-Benzoyl-3-vinyl-4-piperidine]propionic acid ethyl ester

A. A solution of 3.5 g of racemic *cis*-3-[1-benzoyl-3-(2-chloroethyl)-4-piperidine]propionic acid ethyl ester and 2.3 g. of sodium iodide in 120 ml. of methyl ethyl ketone was kept at reflux temperature for 44 hours. The mixture in which a precipitate had formed was diluted with 50 ml. of water and 100 ml. of ether. The organic layer was separated, washed with water, diluted with benzene (100 ml.), dried over anhydrous sodium sulfate, and evaporated to dryness to give 4 g. of liquid racemic *cis*-3-[1-benzoyl-3-(2-iodoethyl)-4-piperidine]propionic acid ethyl ester. This was dissolved in 120 ml. of anhydrous pyridine, and after the addition of 2.5 g. of silver fluoride, the mixture was stirred at room temperature for 24 hours. Ether (800 ml.) was added, and the black precipitate was removed by filtration. The filtrate was washed with 3N aqueous hydrochloric acid (3×) and water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was distilled under a pressure of 0.015 mm Hg to give two fractions: at 120°C. 0.615 g. of 82 percent pure and at 150°C. 0.990 g. of 71 percent pure of liquid racemic *cis*-3-[1-benzoyl-3-vinyl-4-piperidine]propionic acid ethyl ester: yield 38 percent.

B. The mixture of 0.5 g. of racemic *cis*-3-[1-benzoyl-3-(2-chloroethyl)-4-piperidine]propionic acid ethyl ester and glass powder was heated at 190° under a pressure of 0.025 mm. for 5 hours. The black reaction mixture was dissolved in dichloromethane, the glass powder was removed by filtration, and the filtrate was evaporated to dryness. The residue (350 mg.) was distilled at 0.015 mm. Hg and 150°C., to give 99 mg. of liquid, 78% pure, rac. *cis* 3-[1-benzoyl-3-vinyl-4-piperidine]propionic acid ethyl ester.

EXAMPLE 25

3-[1-Benzoyl-3(S)-(2-chloroethyl)-4(S)-piperidine]propionic acid ethyl ester

The mono-*l*-tartrate of 3-[3(S)-ethyl-4(S)-piperidine]-propionic acid ethyl ester (8.9 g.) was treated with excess 2N aqueous potassium carbonate. The liberated free base was extracted into dichloromethane. The combined organic extract was dried over potassium carbonate and evaporated to dryness under reduced pressure to give 5 g. of 3-[3(S)-ethyl-4(S)-piperidine]propionic acid ethyl ester. A solution of the free base in 35 ml. of anhydrous ether was added in a nitrogen atmosphere to a stirred suspension of 3.4 g. of N-chloro-succinimide in 70 ml. of anhydrous ether. After continued stirring for 1 hour at room temperature, the mixture was successively washed with water (3×), 2.5N aqueous sulfuric acid (2×) and water. The etheral solution was dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 5.1 g. of liquid 3-[1-chloro-3(S)-ethyl-4(S)-piperidine]propionic acid ethyl ester. This N-chloroamine was dissolved in 150 ml. of trifluoroacetic acid at 0°. The resulting clear solution was transferred to a quartz flask, purged with dry nitrogen for 30 minutes and then irradiated at 14° with a 200W-Hanovia (Registered Trade Mark) high-pressure mercury lamp. At intervals, samples were removed and the reaction was continued as long as positive starch-iodine test was obtained. After 3 hours the solvent was removed at 35° under reduced pressure. Benzene was added to the residue and evaporated under reduced pressure. This procedure was repeated several times. To a stirred solution of thus obtained 3-[3(S)-(2-chloroethyl)-4(S)-piperidine]propionic acid ethyl ester trifluoroacetate (11.9 g.) and 8 g. of benzoyl chloride in 100 ml. of benzene was added slowly a saturated aqueous solution of potassium carbonate until the mixture reached pH 9. Stirring was continued for 90 minutes. After the addition of 100 ml. of benzene, the mixture was washed successively with 6N aqueous sodium hydroxide (3×), water, 3N aqueous hydrochloric acid and water. The organic layer was separated and dried over anhydrous sodium sulfate. Evaporation to dryness gave 8.4 g. of oily material which was chromatographed on 250 g. of silica gel. Elution with 95:5, 9:1 and 9:2 mixtures of benzene and ethylacetate gave 5.95 g. of liquid, 87 percent pure, 3-[1-benzoyl-3(S)-(2-chloroethyl)-4(S)-piperidine]propionic acid ethyl ester. Yield 60 percent. This product was distilled twice at 0.015 mm Hg and 160°C, to give 2 g. of 98.9 percent pure 3-[1-benzoyl-3(S)-(2-chloroethyl)-4(S)-piperidine]propionic acid ethyl ester: $[\alpha]_D^{22} = -20{,}0°$ (c=0,99, methanol).

EXAMPLE 26

3-[1-Benzoyl-3(S)-vinyl-4(S)-piperidine]propionic acid ethyl ester

A solution of 1.9 g. of 3 - [1 - benzoyl - 3(S) - (2 - chloroethyl) - 4(S) - piperidine]propionic acid ethyl ester and 1.22 g. of sodium iodide in 60 ml. of methyl ethyl ketone was kept at reflux temperature for 50 hours. The mixture in which a precipitate had formed was diluted with 30 ml. of water and 50 ml. of ether. The organic layer was separated, washed with water diluted with benzene (50 ml.), dried over anhydrous sodium sulfate, and evaporated to dryness to give 2.2 g. of liquid crude 3 - [1 - benzoyl - 3(S) - (2 - iodoethyl) - 4(S) - piperidine]propionic acid ethyl ester. This was dissolved in 60 ml. of anhydrous pyridine, and after the addition of 1.3 g. of silver fluoride, the mixture was stirred at room temperature for 20 hours. Ether (400 ml.) was added and the black precipitate was removed by filtration. The filtrate was washed with 3N aqueous hydrochloric acid (3×) and water, dried over anhydrous sodium sulfate and evaporated to dryness. The liquid residue (0.82 g.) was distilled at 0.015 mmHg and 118°C. to give 540 mg. of 75 percent pure 3 - [1-benzoyl - 3(S) - vinyl - 4(S) - piperidine]propionic acid ethyl ester.

EXAMPLE 27

3-[1-Benzoyl-3(R)-(2-chloroethyl)-4(R)-piperidine]propionic acid ethyl ester

The mono-d-tartrate of 3 - [3(R) - ethyl - 4(R) - piperidine]propionic acid ethyl ester (15 g.) was treated with excess 2N aqueous potassium carbonate. The liberated free base was extracted into dichloromethane. The combined organic extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure to give 8.8 g. of 3 - [3(R) - ethyl - 4(R) - piperidine]propionic acid ethyl ester. A solution of the free base in 60 ml. of anhydrous ether was added in a nitrogen atmosphere to a stirred suspension of 6.0 g. of N-chlorosuccinimide in 120 ml. of anhydrous ether. After continued stirring for 1 hour at room temperature, the mixture was successively washed with water (3×), 2.5 N aqueous sulfuric acid (2×) and water. The ethereal solution was dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 9 g. of liquid 3 - [1 - chloro - 3(R) - ethyl - 4(R)-piperidine]propionic acid ethyl ester. This N-chloroamine was dissolved in 150 ml. of trifluoroacetic acid at 0°. The resulting clear solution was transferred to a quartz flask, purged with dry nitrogen for 30 minutes and then irradiated at 10° with 200W-Hanovia (Registered Trade Mark) high pressure mercurcy lamp. At intervals, samples were removed and the reaction was continued as long as a positive starch-iodine test was obtained. After 5 hours, the solvent was removed at 35° under reduced pressure. Benzene was added to the residue and evaporated under reduced pressure. This procedure was repeated several times. To a stirred solution of 3 - [3(R) - (2 - chloroethyl) - 4(R) - piperidine]propionic acid ethyl ester trifluoroacetate (22 g.) and 15 g. of benzoylchloride in 150 ml. of benzene was added slowly a saturated aqueous solution of potassium carbonate until the mixture reached pH 9. Stirring was continued for 1 hour. After the addition of 200 ml. the mixture was washed successively with 6N aqueous sodium hydroxide (3×), water, 3N aqueous hydrochloric acid and water. The organic layer was separated and dried over anhydrous sodium sulfate. Evaporation to dryness gave 18 g. of oily material which was chromatographed on 650 g. of silica gel. Elution with 9:1 mixture of benzene and ethyl acetate gave 11.1 g. of liquid 97.5 percent pure 3 - [1 - benzoyl - 3(R) - (2 - chloroethyl) - 4(R) - piperidine]propionic acid ethyl ester. Yield 74 percent. Analytical sample of 98.6 percent purity was obtained by distillation at 0.018 mmHg and 150°C. $[\alpha]_D^{22} = +20.2°$ (c 1.09, methanol).

EXAMPLE 28

3-[1-Benzoyl-3(R)-vinyl-4(R)-piperidine]propionic acid ethyl ester

A solution of 1.8 g. of 3 - [1 - benzoyl - 3(R) - (2 - chloroethyl) - 4(R) - piperidine]propionic acid ethyl ester and 1.2 g. of sodium iodide in 60 ml. of methyl ethyl ketone was kept at reflux temperature for 44 hours. The mixture in which a precipitate had formed was diluted with 30 ml. of water and 50 ml. of ether. The organic layer was separated, washed with water, diluted with benzene (50 ml.), dried over anhydrous solium sulfate and evaporated to dryness to give 2.3 g of liquid crude 3-[1 - benzoyl - 3(R) - (2 - iodoethyl) - 4(R) - piperidine]propionic acid ethyl ester. This was dissolved in 60 ml of anhydrous pyridine, and after the addition of 1.29 g of silver fluoride the mixture was stirred at room temperature for 15 hours. Ether (400 ml) was added and the black precipitate was removed by filtration. The filtrate was washed with 3*N* aqueous hydrochloric acid (3×) and water, dried over anhydrous sodium sulfate and evaporated to dryness. The liquid residue (1.23 g) was distilled

under a pressure of 0.015 mmHg. A fraction (560 mg.) distilling at 100° (oil bath temperature) contained 94 per cent pure 3 - [1 - benzoyl - 3(R) - vinyl - 4(R)-piperidine]prcpionic acid ethyl ester. By raising the oil bath temperature to 115°, 320 mg. of a second fraction containing 87 percent pure 3 - [1 - benzoyl - 3(R)-vinyl - 4(R) - piperidine]propionic acid ethyl ester was obtained. Total yield 50 percent.

EXAMPLE 29

Preparation of 7′-chlorodihydrocinchonine from 7′-chlorocinchonine

To a solution of 1.06 g of 7′-chlorocinchonine (as dihydrochloride monohydrate) in 500 ml of methanol was added 2.5 ml. of 99% hydrazine hydrate and ca. 10 mg. of cupric sulfate and the mixture was stirred at room temperature in an open flask for 2 days. The methanol was evaporated and the residue partitioned between water and chloroform containing 5% of ethanol, the organic phase was washed (water), dried (sodium sulfate) and evaporated to give 0.8 g of crude product. Crystallization from ethanol-tetrahydrofuran afforded 0.743 g of 7′-chlorodihydrocinchonine; m.p. 278—279° $[\alpha]_D^{20}$ +159.7° (c 0.73 in ethanol-acetic acid 9:1).

EXAMPLE 29a

Preparation of Racemic 5′-Chlorodihydrocinchotoxine from cis-3-(1-benzoyl-3-ethyl-4-piperidine)propionic acid ethyl ester and 6-chloro-4-carbethoxyquinoline

A solution containing 25.4 g. of *cis*-3-(1-benzoyl-3-ethyl-4-piperidine) propionic acid ethyl ester in 250 ml. of dry tetrahydrofuran was added dropwise (30 min.) to a refluxing mixture of 26.9 g. of potassium t-butoxide and 19.0 g. of 6-chloro-4-carbethoxyquinoline under an atmosphere of dry nitrogen. The mixture was heated under reflux for two hours, and the solvent was removed under reduced pressure. The cold residue was dissolved in 300 ml. of 0.5N sodium hydroxide, and washed with four 50 ml. portions of benzene. The combined aqueous phases containing the β-ketoester were acidified (conc. HCl) whereby a 6N hydrochloric acid solution was obtained, and then heated under reflux for 20 hours. The cooled reaction mixture was made alkaline with 6N sodium hydroxide, and extracted with ether. The ethereal extracts were dried over anhydrous potassium carbonate and evaporated to dryness. The product (17.3 g.) was absorbed on 500 g. of neutral alumina, activity II. Elution with benzene and with dichloromethane removed some less polar impurities. Elution with methanol yielded 13.6 g. (51%) of amorphous racemic 6′-chlorodihydrocinchotoxine.

EXAMPLE 29b

Preparation of a Mixture of racemic 6′-Chlorodihydrocinchonidinone and Racemic 6′-Chlorodihydrocinchoninone from Racemic 6′-Chlorodihydrocinchotoxine

To a solution containing 13.6 g. of racemic 6′-chlorodihydrocinchotoxine in 200 ml. of dichloromethane was added 18 ml. of about a 17% aqueous sodium hypochlorite and the mixture was stirred for 60 min. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate and concentrated to a volume of about 20 ml. This solution, containing the chloramine, was added dropwise to 60 ml. of 99.5% phosphoric acid. The solvent was evaporated, and the viscous mixture was stirred at 20° for 17 hours. The mixture was diluted with water, and made alkaline with 6N potassium hydroxide. The alkaline aqueous phase was kept at about 70° for 30 min., and, thereafter, it was extracted thoroughly with ether. The ethereal phase was dried over anhydrous potassium carbonate and concentrated to dryness. The product (11.7 g.) was absorbed on 100 g. of neutral alumina, activity II. Elution with benzene and dichloromethane yielded 9.3 g. (69%) of racemic 6′-chlorodihydrocinchonidinone and racemic 6′-chlorodihydrocinchoninone which was crystallized from hexane to give 7.56 g. of a product having a melting point of 97.5—100.5° containing some chlorine free impurity. A crystalline mixture of racemic 6′-chlorodihydrocinchonidinone and racemic 6′-chlorodihydrocinchoninone was prepared by reoxidizing a mixture of racemic 6′-chlorodihydrocinchonine and racemic 6′-chlorodihydrocinchonidine.

EXAMPLE 29c

Preparation of Racemic 6′-Chlorodihydrocinchonidine and Racemic 6′-Chlorodihydrocinchonine from a mixture of Racemic 6′-Chlorohydrocinchonidinone and Racemic 6′-Chlorodihydrocinchoninone

To a solution of 6.73 g. of a mixture of the racemic 6′-chlorodihydrocinchonidinone and racemic 6′-chlorodihydrocinchoninone (material melting at 97.5—100°) in 200 ml. of dry benzene, stirred under an atmosphere of dry nitrogen at 20°, was added dropwise a 35% solution of di-isobutyl aluminium hydride in toluene. After

addition of 13 ml., the reaction was completed. The reaction was quenched by addition of 20 ml. of methanol-water (2:3). The precipitated alumina was separated by filtration and washed thoroughly with benzene. The filtrates were combined. The benzene layer separated and dried over anhydrous sodium sulfate and evaporated to dryness. The product (6.7 g.) could not be crystallized, therefore it was separated by preparative thin layer chromatography (silica gel GF_{254}; chloroform-triethylamine = 9:1) into three fractions.

The least polar fraction (1.34 g.) was crystallized and recrystallized from acetone to give racemic 6'-chlorodihydrocinchonine having a melting point of 172.5—173.5°. Racemic 6'-chlorodihydrocinchonine dihydrochloride had a melting point of 218—221° (dec.).

The middle fraction (2.83 g.) was crystallized from acetone to give racemic 6'-chlorodihydrocinchonidine having a melting point of 100—102°.

Racemic 6'-chlorodihydrocinchonidine dihydrochloride had a melting point of 219—222° (dec.) (recrystallized from methanol-ether).

The most polar fraction (1.42 g.) was crystallized from ethanol to give a mixture of chlorine free racemic dihydrocinchonine and racemic dihydrocinchonidine having a melting point of 190—192.5°.

Example 29d

Preparation of Racemic 6'-Methyldihydrocinchotoxine from cis-3-(1-benzoyl-3-ethyl-4-piperidine)propionic acid ethyl ester and 6-methyl-4-carbethoxyquinoline

A solution containing 19.6 g. of *cis*-3-(1-benzoyl-3-ethyl-4-piperidine)propionic acid ethyl ester in 600 ml. of dry benzene was added dropwise (3-1/2 hours) to a refluxing mixture comprising 20.3 g. of 6-methyl-4-carbethoxyquinoline and 20.8 g. of potassium t-butoxide in 300 ml. of dry benzene under an atmosphere of dry nitrogen. The mixture was heated under reflux for an additional hour and maintained at 20° overnight. The crude mixture was extracted once with 200 ml. and three times with 20 ml. of cold 0.5N aqueous potassium hydroxide. Thereafter, the aqueous phases were washed with 4 portions of 50 ml. of benzene. The combined alkaline aqueous phases containing the crude β-ketoester were acidified with conc. HCl whereby a 6N hydrochloric acid solution was obtained, and then heated under reflux for 24 hours. The cooled mixture was made alkaline with 6N potassium hydroxide, and extracted with ether. The ethereal extracts were dried over anhydrous potassium carbonate and evaporated to dryness to give 13.1 g. (68%) of racemic 6'-methyldihydrocinchotoxine.

Example 29e

Preparation of a Mixture of racemic 6'-Methyl-dihydrocinchonidinone and racemic 6'-Methyl-dihydrocinchoninone from racemic 6'-Methyl-dihydrocinchotoxine

To a solution containing 13.1 g. of racemic 6'-methyl-dihydrocinchotoxine in 150 ml. of dichloromethane was added an excess of about 17% aqueous sodium hypochlorite solution, and the mixture was stirred at 20° for 1 hour. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate and concentrated to 20 ml. This solution, containing the chloramine, was added dropwise to 50 ml. of 99.5% phosphoric acid. The dichloromethane was evaporated, and the viscous mixture was stirred at 20° for 17 hours. Thereafter, the mixture was diluted with 20 ml. of water and made alkaline with 6N potassium hydroxide. The alkaline aqueous phase was maintained at 40° for 30 min. and subsequently extracted with dichloromethane. The organic extracts were dried over anhydrous sodium sulfate and concentrated to dryness to give 13.2 g. of a crystalline product. A portion was recrystallized twice from hexane to give about a 1:1 mixture of 6'-methyl-dihydrocinchonidinone and racemic 6'-methyl-dihydrocinchoninone having a melting point of 105—108°.

Example 29f

Preparation of Racemic 6'-Methyl-dihydrocinchonidine and racemic 6'-Methyl-dihydrocinchonine from a mixture of racemic 6'-Methyl-dihydrocinchonidinone and racemic 6'-Methyl-dihydrocinchoninone

12.3 g. of a mixture comprising the ketones racemic 6'-methyl-dihydrocinchonidinone was reduced in several batches. In a typical run 4.0 g. of crystalline mixture was dissolved in 125 ml. of dry benzene, and 9 ml. of a 25% solution of di-isobutyl aluminum hydride was added dropwise at 20° to the stirred solution under an atmosphere of dry nitrogen. After about 30 min., the reaction was quenched by addition of 15 ml. of aqueous methanol (2:3). The precipitated alumina was separated by filtration

and washed thoroughly with benzene. The filtrates were combined, and the benzene layer separated, dried over anhydrous sodium sulfate and evaporated to dryness. Trituration with acetone yielded crystalline 6'-methyl-dihydrocinchonidine having a melting point of 216—218° after recrystallization from tetrahydrofuran.

Racemic 6'-methyl-dihydrocinchonidine dihydrochloride was crystallized from methanol-ether, m.p. 213—216° (dec.).

The mother liquors were converted to the dihydrochloride, whereupon 2.8 g. of racemic 6'-methyl-dihydrocinchonine dihydrochloride was crystallized from methanol and had a melting point of 219—220° (dec.).

A portion was converted to the free base and crystallized from acetone to give racemic 6'-methyl-dihydrocinchonine having a melting point of 153.5—155°.

Example 29g

Preparation of a mixture of racemic 6'-Methyl-dihydroepicinchonidine and of racemic 6'-Methyl-dihydroepicinchonine, racemic 6'-Methyl-dihydrocinchonidine and racemic 6'-Methyl-dihydrocinchonine from a mixture of racemic 6'-Methyl-dihydrocinchonidinone and 6'-Methyl-dihydrocinchoninone

To an ice cold solution of 0.308 g. of a mixture of racemic 6'-methyl-dihydrocinchonidinone and racemic 6'-methyl-dihydrocinchoninone in 20 ml. of methanol was added 0.3 g. of solid sodium borohydride, and the resulting solution was stirred at 0° for 60 min. Water (10 ml.) was added, and the methanol was evaporated *in vacuo*. The aqueous residue was extracted thoroughly with dichloromethane. The organic extracts were dried over sodium sulfate and evaporated to dryness to give 0.291 g. of product, which was separated by preparative layer chromatography (silica gel GF_{254}; chloroform: triethylamine: methanol = 89:10:1) into 0.157 g. (50.5%) of an amorphous, inseparable mixture of racemic 6'-methyl-dihydroepicinchonidine and racemic 6'-methyl-dihydroepicinchonine, 0.020 g. (6.5%) of racemic 6'-methyl-dihydrocinchonine and 0.023 g. (7.5%) of racemic 6'-methyl-dihydrocinchonidine.

Example 30
Tablet Formulation

	Per Tablet
Racemic 7'-methoxy-dihydrocinchonidinone	25.00 mg
Dicalcium Phosphate Dihydrate, Unmilled	175.00 mg
Corn Starch	24.00 mg
Magnesium Stearate	1.00 mg
Total Weight	225.00 mg

Procedure:

25 Parts of racemic 7'-methoxy-dihydrocinchonidinone and 24 parts of corn starch were mixed together. This premix was then mixed with 175 parts of dicalcium phosphate and one-half part of magnesium stearate, passed through a No. 1A screen and slugged. To the slugs was added the remaining magnesium stearate. The mixture was mixed and compressed.

Example 31
Capsule Formulation

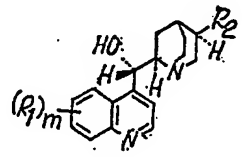
	Per Capsule
Racemic 7'-methoxy-dihydrocinchonidinone	50.00 mg
Corn Starch	150.00 mg
Talc	10.00 mg
Total Weight	210.00 mg

Procedure:

Fifty parts of racemic 7'-methoxy-dihydrocinchonidinone were mixed with 150 parts of corn starch in a suitable mixer. The mixture was further blended. The blended powder was returned to the mixer and 10 parts of talc were added and blended thoroughly. The mixture was filled into No. 4 hard shell gelatin capsules on a Parke Davis capsulating machine.

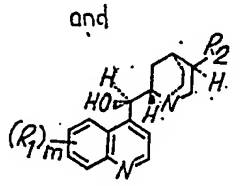
WHAT WE CLAIM IS:—

1. A process for the manufacture of quinoline derivatives of the general formulae



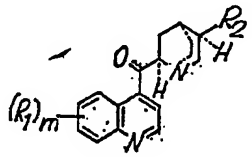
I

and



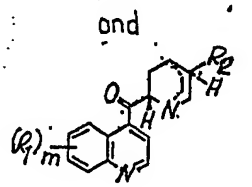
II

wherein R_1 is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or methylenedioxy, R_2 is lower alkyl or lower alkenyl and m is the integer 1 or 2, with the proviso that when R_1 is methylenedioxy m is the integer 1, of their antipodes and racemates and acid addition salts thereof, which process comprises treating compounds of the general formulae



V

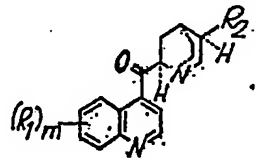
and



VI

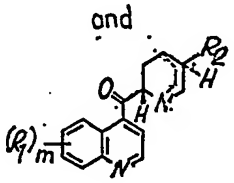
wherein R_1, R_2 and m have the meanings given earlier in this claim, their antipodes or racemates thereof with a stereoselective reducing agent, if desired reducing any compound obtained in which R_2 is a lower alkenyl group to give a corresponding compound in which R_2 is a lower alkyl group and, also if desired, converting bases obtained into acid addition salts.

2. A process for the manufacture of quinoline derivatives of the general formulae



V

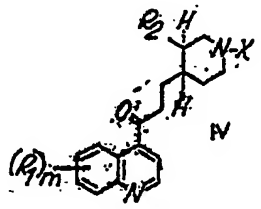
and



VI

wherein R_1 is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or methylenedioxy, R_2 is lower alkyl or lower alkenyl and m is the integer 1 or 2, with the proviso that when R_1 is methylenedioxy m is the integer 1,

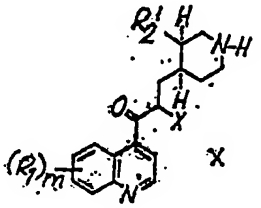
of their antipodes and racemates and acid addition salts thereof, which process comprises cyclizing a compound of the general formula



IV

wherein R_1, R_2 and m have the meanings given earlier in this claim and X is halogen, with the proviso that when $(R_1)_m$ is hydrogen or a methoxy group in position 6' and R_2 is vinyl or ethyl, X is other than bromine,

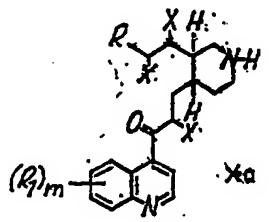
or antipodes or racemates thereof, or a compound of the general formula



X

wherein R_1, X and m have the meanings given earlier in this claim and R'_2 is lower alkyl,

or antipodes or racemates thereof, or a compound of the general formula



Xa

wherein R_1, X and m have the meanings given earlier in this claim and R is hydrogen or alkyl with 1 to 5 carbon atoms,

or antipodes or racemates thereof, by means of a cyclization agent, dehalogenating the cyclization product obtained from a compound of formula Xa or antipodes or racemates thereof and, if desired, converting the so obtained bases into acid addition salts.

3. A process according to claim 1, wherein a dilower alkyl aluminium hydride is used as the stereoselective reducing agent.

4. A process according to claim 1 or claim 3, wherein di-*iso*butyl aluminium hydride is used as the stereoselective reducing agent.

5. A process according to claim 1, claim 3 or claim 4, wherein the stereoselective reduction is carried out at a temperature between 20°C and 50°C.

6. A process according to claim 1, claim 3, claim 4 or claim 5, wherein the reduction of the lower alkenyl group is carried out with diimine.

7. A process according to any one of claims 1 and 3 to 6 inclusive wherein a compound of formula V or VI in which R_2 is vinyl or ethyl and $(R_1)_m$ is hydrogen, lower alkyl, methoxy or halogen in position 6′ or 7′ or in positions 6′ and 7′ or antipodes or racemates thereof is used as the starting material.

8. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 7-methoxy - 4 - [5(R) -ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl]-quinoline, its antipode or racemate thereof is used as the starting material.

9. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 7-methoxy - 4[5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

10. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6,7-dimethoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

11. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6,7 - dimethoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

12. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6-methyl - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

13. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6-methyl - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

14. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6-chloro - 4[5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

15. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6-chloro - 4[5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

16. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 7 - chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R)- ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

17. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 7-chloro - 4 - [5(R) - ethyl - 4(S) - quinclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

18. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 7 - chloro - 4 - [5(R) - vinyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

19. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 7-chloro - 4 - [5(R) - vinyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

20. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6-methoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

21. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6-methoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

22. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6-methoxy - 4 - [5(R) - vinyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

23. A process according to any one of claims 1 and 3 to 7 inclusive, wherein 6-methoxy - 4 - [5(R) - vinyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl] - quinoline, its antipode or racemate thereof is used as the starting material.

24. A process according to claim 2, wherein the cyclizing agent is an organic or inorganic acid or an organic base.

25. A process according to claim 2 or claim 24, wherein phosphoric acid or sulfuric acid, trichloroacetic or trifluoroacetic acid is used as the acidic cyclizing agent.

26. A proess according to claim 2 or claim 24, wherein an alkali metal alkoxide is used as the basic cyclizing agent.

27. A process according to claim 2, claim 24 or claim 25, wherein sodium ethoxide in ethanol or sodium methoxide in methanol is used as the basic cyclizing agent.

28. A process according to any one of claims 2 or 24 to 27 inclusive, wherein the reaction is carried out at a temperature of between 20°C and 50°C.

29. A process according to any one of claims 2 or 24 to 28 inclusive, wherein a compound of formula IV in which X is chlorine, R_2 is vinyl or ethyl and $(R_1)_m$ is hydrogen, halogen or methoxy in position 6′ or 7′ or positions 6′ and 7′ is used as the starting material.

30. A process according to any one of claims 2 or 24 to 29 inclusive, wherein 6 - methoxy - 4 - [3 - (1 - chloro - 3(R) - ethyl - 4(R) - piperidyl) - 1 - oxopropyl] - quinoline, its antipode or racemate thereof is used as the starting material.

31. A process according to any one of claims 2 or 24 to 29 inclusive, wherein 7-methoxy-4-[3-(1-chloro-3(R)-ethyl-4(R)-piperidyl)-1-oxopropyl]-quinoline, its antipode or racemate thereof is used as the starting material.

32. A process according to any one of claims 2 or 24 to 29 inclusive, wherein 6-methoxy-4-[3-(1-chloro-3(R)-vinyl-4(R)-piperidyl)-1-oxopropyl]-quinoline, its antipode or racemate thereof is used as the starting material.

33. A process according to any one of Claims 2 or 24 to 29 inclusive, wherein 6,7-dimethoxy-4-[3-(1-chloro-3(R)-ethyl-4-(R)-piperidyl)-1-oxopropyl]-quinoline, its antipode or racemate thereof is used as the starting material.

34. A process according to any one of claims 2 or 24 to 29 inclusive, wherein 6-methyl-4-[3-(1-chloro-3(R)-ethyl-4(R)-piperidyl)-1-oxopropyl]-qiunoline, its antipode or racemate thereof is used as the starting material.

35. A process according to any one of claims 2 or 24 to 29 inclusive, wherein 6-chloro-4-[3-(1-chloro-3(R)-ethyl-4(R)-piperidyl)-1-oxopropyl]-quinoline, its antipode or racemate thereof is used as the starting material.

36. A process according to any one of claims 2 or 24 to 29 inclusive, wherein 7-chloro-4-[3-(1-chloro-3(R)-ethyl-4(R)-piperidyl)-1-oxopropyl]-quinoline, its antipode or racemate thereof is used as the starting material.

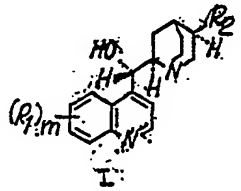
37. A process according to any one of claims 2 or 24 to 29 inclusive, wherein 7-chloro-4[3-(1-chloro-3(R)-vinyl-4(R)-piperidyl)-1-oxopropyl]-quinoline, its antipode or racemate thereof is used as the starting material.

38. A process for the manufacture of quinoline derivatives, substantially as hereinbefore described with reference to the foregoing Examples 1—3, 6—8, 20, 21, 21b, 21c, 29, 29b, 29c and 29e—g.

39. Quinoline derivatives of formulae I and II given in claim 1, their antipodes and racemates and acid addition salts thereof, when manufactured according to the process claimed in any one of claims 1 and 3 to 7 inclusive.

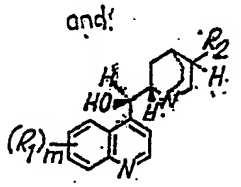
40. Quinoline derivatives of formulae V and VI in claim 2, their antipodes and racemates and acid addition salts thereof, when manufactured by the process claimed in any one of claims 2 and 24 to 28 inclusive.

41. Quinoline derivatives of the general formulae



I

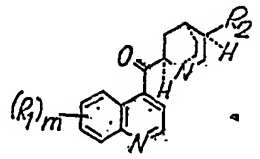
and



II

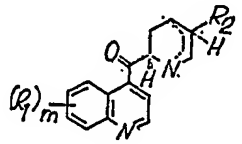
wherein R_1 is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or methylenedioxy, R_2 is lower alkyl or lower alkenyl and m is the integer 1 or 2, with the proviso that when R_1 is methylenedioxy m is the integer 1, and with the proviso that when $(R_1)_m$ is hydrogen, hydroxy or a lower alkoxy group in position 6' R_2 is other than vinyl or ethyl,
their antipodes and racemates and acid addition salts thereof.

42. Quinoline derivatvies of the general formulae



V

ond



VI

wherein R_1 is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or methylenedioxy, R_2 is lower alkyl or lower alkenyl and m is the integer 1 or 2, with the proviso that when R_1 is methylenedioxy m is the integer 1, and with the proviso that when $(R_1)_m$ is hydrogen, hydroxy or a methoxy group in position 6' R_2 is other than vinyl or ethyl,
their antipodes and racemates and acid addition salts thereof.

43. 6 - Methoxy - α(S) - [5(R) - propyl - 4(S) - quinuclidin - 2(R) - yl] - 4 - quinolinemethanol, its antipode and racemate and acid addition salts thereof.

44. 6 - Methoxy - α(R) - [5(R) - allyl - 4(S) - quinuclidin - 2(S) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

45. 7 - Methoxy - α(S) - [5(R) - ethyl - 4(S) - quinuclilin - 2(R) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

46. 7 - Methoxy - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

47. 6,7 - Dimethoxy - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

48. 6,7 - Dimethoxy - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

49. 6 - Methyl - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

50. 6 - Methyl - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

51. 6 - Chloro - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

52. 6 - Chloro - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

53. 7 - Chloro - α(S) - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

45. 7 - Chloro - α(R) - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

55. 7 - Chloro - α(S) - [5(R) - vinyl - 4(S) - quinuclidin - 2(R) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

56. 7 - Chloro - α(R) - [5(R) - vinyl - 4(S) - quinuclidin - 2(S) - yl] - 4- quinolinemethanol, its antipode and racemate and acid addition salts thereof.

57. 7 - Methoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl] - quinoline, its antipode and racemate and acid addition salts thereof.

58. 7 - Methoxy - 4[5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl] - quinoline, its antipode or racemate and acid addition salts thereof.

59. 6,7 - Dimethyl - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl]-quinoline, its antipode or racemate and acid addition salts thereof.

60. 6,7 - Dimethoxy - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl]-quinoline, its antipode or racemate and acid addition salts thereof.

61. 6 - Methyl - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl]-quinoline, its antipode or racemate and acid addition salts thereof.

62. 6 - Methyl - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl]-quinoline, its antipode or racemate and acid addition salts thereof.

63. 6 - Chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl]-quinoline, its antipode or racemate and acid addition salts thereof.

64. 6 - Chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl]-quinoline, its antipode or racemate and acid addition salts thereof.

65. 7 - Chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(R) - ylcarbonyl]-quinoline, its antipode or racemate and acid addition addition salts thereof.

66. 7 - Chloro - 4 - [5(R) - ethyl - 4(S) - quinuclidin - 2(S) - ylcarbonyl]-quinoline, its antipode or racemate and acid addition salts thereof.

67. A pharmaceutical preparation comprising a quinoline derivative as claimed in claim 41, an antipode, racemate or acid addition salt thereof in association with a compatible pharmaceutical carrier.

68. A pharmaceutical preparation comprising a quinoline derivative as claimed in claim 42, an antipode, racemate or acid addition salt thereof in association with a compatible pharmaceutical carrier.

For the Appplicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
24 Southampton Buildings,
Chancery Lane,
London, W.C.2.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1971.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.